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THE CORRELATION OF UNIVERSITY RESEARCH *

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There has been some criticism of the medical profession during the past twenty-five years for its tendency toward specialization; no comments are needed here as to why this has occurred. In this respect, medicine does not differ from engineering, chemistry, and to some extent the law. As far as the physical welfare of the patient is concerned, there is no doubt in my mind that it is better protected by specialization, especially with the increased efficiency in correlation. In my opinion, conditions could be still further enhanced by better bridging of the gap between the clinician and the research worker, and the much wider expanse that seems to exist in research between various special departments in our universities.

Today I expect to take full advantage of the prerogatives of the Chair to present a few thoughts that have interested me for a number of years and which were formulated and recorded some five years ago. These thoughts do not pertain strictly to ophthalmology or even to medicine but more strictly to university research in which the various branches of medicine would be included, and few more than the eye.

During the past ten years there has been some discussion as to whether research was not drifting away from our universities and centering in the laboratories of certain of the larger corporations. Many of us are not wholly in accord with this view, although we must realize that for obvious reasons these laboratories do harbor a splendid corps of research workers devoting their time to pure and applied science and with excellent results.

Within the past nine months most of us have heard of the importance and inconvenience of frozen financial accounts, but to estimate the number and importance of frozen scientific accounts is a more difficult matter. As is well known, most departments in the university of today maintain their own individual research laboratories; this is as it should be, but it seems to me that there might be a broadening of their endeavors so as to provide greater research contacts such as could be available in our larger institutions. Would it be possible to accomplish this by providing a centralized or university research laboratory administered by a small group of full time research workers, which laboratory would be available for research workers from any department of the university, in other words full and part time departmental fellowships? In addition to these, facilities could be provided for certain industries without laboratory conveniences, should they desire to have certain problems investigated. Needless to say, the results of such investigations should be published.

While moving pictures have been used for scientific and teaching purposes to some extent for a number of years, their use has been distinctly limited and less than their real value would warrant. During the next five years their use will greatly increase. Therefore such a laboratory should include a moving picture studio available to any department of the university desiring to film scientific work, methods of procedure and material for demonstration that would be suitable for scientific exhibition or teaching purposes. Needless to say, a research department pertaining to the various phases of this subject should be established. It might be difficult to designate appropriately such a laboratory as is here projected, but a "research laboratory of physics and chemistry" would probably best cover what I have in mind.

If there is value in correlation in departmental clinical work, why not in the broader sense of university research work? Such a laboratory would bring together under one roof investigators working on the same subjects, but each especially interested in the phase peculiar to his own department. It would permit of intimate correlation between various departments on certain problems that have a dual aspect. It would not interfere with departmental laboratories but would really supplement such work and, it is believed, would be a real stimulus to research. Would not such a laboratory with its multiplicity of contacts be a chosen field for graduate work in pertinent medical research? From this constant 'rubbing of elbows' would not both science and investigator be benefited?

Such a laboratory would deal with acoustic energy and the whole range of radiant energy from the infra-red to the more recently discovered Millikan ray. This would include all phases of illumination, health problems as these relate to the curative or injurious effects of various types of radiation, x-rays, and the many phases pertaining to radio communication, the telephone and the phonograph, vocal and instrument music, and inorganic, organic and biochemistry. There is much that is desirable still to be accomplished in the movies, such as the perfection of color films, the third dimension and the correlation of sound. The coordination of the voice with television opens up a field for investigation for years to come.

As to chemistry, our greatest interest is in the biochemical phase. For some years I have pointed out to many of the younger men with whom I have come in

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* Chairman's address, read before the Section on Ophthalmology at the Eighty-First Annual Session of the American Medical Association, Detroit, June 25, 1930.

contact the possibilities of this science in ophthalmology. Until a few years ago but little work had been done in this subject, the one from which will emanate, unless I am much mistaken, the real advances in the ophthalmology of the future. From this source will come the facts that will influence the medical and surgical treatment of such conditions as cataract, certain types of glaucoma and other ocular diseases. While I am aware that splendid work has been and is being done in chemistry as well as the other sciences in the departmental laboratories, I still feel that both the investigator and the science which he represents would be benefited by more intimate working contacts and the exchange of ideas and knowledge that these provide.

The possibilities of this conception are too numerous and too evident to detail to a group of my peers, but I merely desire to point out that such a project would have its relationship and interest to practically all industries, from that of the one great national industry that fosters child labor, the public school, to our largest corporations of whatever character, as well as to all professions. As remote as it may seem, it is conceivable that the construction engineer, the architect, the aurist, the musician and the electrician have certain problems in sound wherein experimental work would profit by an exchange of thoughts peculiar to their individual pursuits, yet pertinent to their common interest. So, too, we can conceive that the comparative studies of the influences of visible and invisible light on the products and pathology of animal and plant life would afford interest to most branches of medicine, the biologist, botanist, psychologist and chemist. From a medical standpoint, not a respectable surface scratch has been made on the adaptability of the movies in physiologic, bacteriologic, experimental or microscopic work in general. But this is sufficient briefly and grossly to project my thoughts, and those who might be interested can readily conjure up others. To those who are not interested, I offer as an excuse for presenting this subject the fact that if the optical properties of the eye, so admirably adapted to one of the types of energy to which I referred, should be eliminated, little would remain that appeals more than in any other organ in the body, and most pathologic manifestations of the eye are secondary to diseases originating in adjacent or distant organs. Ophthalmologists are a unit in the science and art of medicine, and as such should be interested in the welfare of medical science as a whole. Should this link that binds us to medicine be broken, my interest in the subject to which I have devoted many difficult but happy hours would cease.

1819 Chestnut Street.

Anatomy.—The day when the medical student enters the dissecting room is the time of dedication to his profession, for then he puts his hand to a task which other men dread and joins the company of those who had laid aside the deepest fears and prejudices of mankind to seek in the dead bodies of their fellows some increase of knowledge wherewith to fight the ignorance and disease that laid them low. As he undertakes his share of this work the student of anatomy engages in one of the oldest of the sciences. He is following a tradition of twenty five centuries and if he is sensitive to such influences, the burden of his work will be lightened and his effort will be quickened by a sense of pride that he is one of that profession whose history is an endless record of hard won progress from darkness towards the light. Whether we feel it thus keenly or not, however, the influence of the past inevitably guides our hands as we work.—Corner, G. W.: Clio Medica—Anatomy, New York, Paul B. Hoeber, Inc., 1930.

THE PRESENT STATUS OF NONSPECIFIC THERAPY

THE FRANK BILLINGS LECTURE*

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About twenty years ago I dined with a surgeon from California. This was during the heyday of specific vaccine therapy. We discussed the use of vaccines and especially their shortcomings. He had a theory that the poor results were due to the role played by mixed infections in this group of diseases and thought that greater benefit could be obtained by using mixed vaccines. He was a horse fancier, and an epidemic of epizootic gave him an opportunity to apply his theory. He transferred some of the nasal secretions from a sick horse to a beer bottle containing beef tea, which he then incubated. After obtaining a number of such cultures, he poured them all into a flask, sterilized them by heat, filtered them and used this filtrate intravenously. He claimed that by this treatment epizootic could be promptly aborted.

He then took pus from his septic surgical patients, again using his beef tea and beer bottle, finally mixing all his cultures, sterilizing them by heat and filtering. The sterilized filtrate was put up in small bottles holding between 5 and 10 cc. He showed me records of a number of patients suffering from acute febrile conditions, in whom the disease had apparently subsided after one or two intravenous injections. He advised, however, that the treatment be given daily until the patient no longer reacted with a chill.

He did not lay any claim to a knowledge of bacteriology, but I was impressed by his keen powers of observation and his apparent honesty. He asked me to try out his remedy. The day following, we visited the county hospital for the purpose of using his vaccine on some patients with acute arthritis. He assured me that he had never observed any untoward results.

Two patients with acute polyarthritis and one with a gonorrheal infection of the knee were given an intravenous injection of this vaccine. The following day we revisited the hospital. He was optimistic, I skeptical. I was surprised, however, to find all of his patients free from pain and swelling and with practically all evidence of the disease gone. The Negro patient with the gonorrheal arthritis, in spite of having broken a tooth during the chill, was jubilant, as the pain and stiffness in the knee had quite disappeared. This was my introduction to nonspecific therapy.

He left me a liberal supply of his vaccine, and shortly after this he disposed of his product to a wholesale drug manufacturer, who placed it on the market under the trade name of Phylacogen.

As autogenous vaccines were the vogue, this treatment was distinctly unorthodox. However, the favorable effect of the vaccine was undeniable. A few years later, in 1914, two articles appeared almost simultaneously, one from Japan and the other from South America, which at least in part cleared up this enigma. Ichikawa reported that typhoid could be aborted by the intravenous injection of either typhoid or paratyphoid vaccine. Kraus and Mazya from Argentina reported that colon bacillus vaccine, given intravenously, would abort typhoid This marks the beginning of nonspecific vaccine therapy The following year Lüdke demonstrated that the same results could be obtained by using a solution of proteose Hence the name "protein therapy"

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* Read before the Section on Practice of Medicine at the Eighty-First Annual Session of the American Medical Association, Detroit, June 27, 1930.

PROTEIN THERAPY

More recently, numerous agents have been recommended as having a common property—the ability to cause a marked febrile reaction Apparently, it is a matter of indifference what substance is employed, as it is the reaction, and not the agent causing it, that is responsible for the results

It is believed that this reaction promotes the mobilization of both specific and nonspecific immune bodies It is quite probable that the body has a reserve store of nonspecific antibodies for emergencies It is not improbable that the initial chill of an acute infection may be a purposeful reaction Old medical literature contains numerous references to the beneficial effects of a secondary infection in acute diseases An attack of erysipelas might benefit tuberculosis of the skin or syphilis

In 1883, Fehleisen reported the cure of lupus following the local injection of a pure culture of streptococci from a case of erysipelas Emmerich, in 1886, was able to save animals with anthrax by the intravenous injection of living streptococci Powlowski, a student of Virchow's, observed similar cures in anthrax following the injection of cultures of the bacillus of Friedlander, *B pyocyaneus*, and other bacteria Buchner, in 1890, showed that killed cultures of these bacilli were equally efficient Following Frankel's report on the value of typhoid vaccine given subcutaneously in typhoid, Rumpf demonstrated that the same results could be obtained by repeated intramuscular injections of large doses of pyocyaneus vaccine

The great improvement in psychiatric patients, following some intercurrent acute infection, led Wagner Jauregg, forty years ago, to attempt to duplicate this infection in patients with dementia paralytica Finally, after many years of patient effort, he was able to report the startling results he had obtained by inoculating the patient with malaria

It is reported that Hippocrates and Galen recognized the beneficial results of fever in psychosis Boerhaave and Sydenham reported similar observations Among the various intercurrent infections reported to have served this purpose are typhoid, typhus, intermittent fever, cholera, smallpox, erysipelas, scarlatina, measles, pneumonia and chronic suppurative processes Koster, in 1848 reported psychoses in patients, several of whom recovered following an attack of relapsing fever Kostl in 1853, reported a cure or, at least, great improvement in a case of dementia paralytica after the patient had had smallpox Schlager, in 1857, reported six psychotic patients out of eleven cured after having had typhoid Many more observations of a similar character are reported by Gerstmann in his monograph on the treatment of dementia paralytica by malarial inoculation

Protein therapy has been employed in nearly all acute and chronic diseases of supposed bacterial origin At present it is used especially in acute polyarthritis gonorrheal arthritis the infectious type of chronic arthritis during the period of more or less active inflammation, acute iritis corneal ulcer, thrombo-angiitis obliterans, bacillary dysentery, dementia paralytica, and multiple sclerosis

Probably the most dramatic results are observed in acute polyarthritis, and it is safe to say this is the only method of treatment that can immediately terminate this disease, at least 50 per cent of patients can be promptly relieved of their discomfort About one half of them are cured, the others, after a few days or occasionally a week or more, have a recurrence In the others the immunity is complete Whether the immunity is complete or partial is an individual affair, dependent on the patient's ability to store or mobilize immune bodies If the patient shows a good response to the first two reactions, the treatment is continued at two-day intervals until five doses have been given I have tried continuing the treatment after all symptoms have subsided, in the hope that recurrences might be lessened but without success In case no improvement is noted after two good reactions, the treatment is discontinued, as rarely will longer continued treatment prove beneficial

In the early stages of chronic atrophic arthritis, in which there is marked evidence of inflammation, this treatment will occasionally give gratifying results, terminating the disease, occasionally permanently, more frequently for a few months, after which it again becomes active but will usually yield to a second course of treatment I have had a few patients in whom there has been no evidence of recurrence after several years with the characteristic spindle shaped fingers remaining as evidence that the diagnosis was correct

It is highly improbable that protein therapy is of permanent value in ostearthritis, as mechanical irritation, rather than bacterial infection, is the important etiologic factor

As thrombo-angiitis obliterans is due to an inflammatory reaction, probably of bacterial origin, it offers a field for protein therapy If this treatment is begun early in the course of the disease, the results may be most gratifying Not only is its progress stopped, but the patient may show great improvement in his ability to walk without discomfort, in fact, the pain may entirely disappear, although in no instance in which the dorsalis pedis is obliterated have I observed a return of the pulse The treatment however, may stop the inflammation in some of the collateral vessels, with subsequent return of function A patient who had this disease in one foot was treated with typhoid vaccine, the symptoms all subsided Several years later the disease appeared in the other foot In the more advanced cases, transitory relief due to vasodilatation may be observed

In southeastern Europe, protein therapy has been used quite extensively in the treatment of bacillary dysentery and is reported to be much more efficient than the dysentery serum

I have used immunized chicken serum, normal chicken serum and immunized sheep serum in the treatment of pneumonia These serums frequently, but not always gave a chill It was noted that when the patient failed to react by a rise in temperature there was no change in the course of the disease Occasionally, after a violent reaction the disease would terminate by crisis The immunized chicken serum after the fibrin was removed, would no longer cause a marked change in temperature and failed to modify the course of the disease

I thought it might be of interest to determine whether a single small dose of typhoid vaccine intravenously sufficient to give a moderate reaction, would modify the course of pneumonia Fifteen patients with lobar pneumonia were so treated within forty-eight hours of the onset of the disease Three of these, or 20 per cent, had an immediate and lasting crisis with disappearance of all symptoms The lung, however, failed to undergo resolution until the regular time for the crisis This experiment was made, not for the purpose of advising this treatment in pneumonia, but merely to remind those interested in pneumococcous serum that recovery following a serum, if accompanied by a rise in temperature, was not evidence of the specific reaction of the serum

The greatest interest in protein therapy is now centered in its use in the treatment of dementia paralytica Although others had observed striking improvement in dementia paralytica following various acute infections, Wagner-Jauregg—if not the first—was the most persistent in imitating nature's method He first tried to inoculate patients with erysipelas but was able to cause only *a circumscribed infection in the skin* He next used tuberculin but was unable to obtain repeated marked changes in temperature However, he persisted in this treatment and after ten years reported the results in sixty-nine patients He thought that he had been able in many of these to produce more frequent and more prolonged remissions but no cures He then tried larger doses of tuberculin With this modification, he obtained a few lasting remissions the patients were able to leave the institution and return to work Whether the improvement was permanent in any of these cases is not recorded

Later, Wagner-Jauregg used Besredka's polyvalent typhoid vaccine, which contained living typhoid bacilli whose virulence had been reduced by mixing with typhoid immune serum This vaccine was given intravenously in increasing doses The frequency, degree and duration of the remissions were much better than with tuberculin

He inoculated his first patients with malaria in 1917 Two of the four patients who were treated at this time, and who showed marked improvement, were still working at their former occupations in 1925

It has been shown that, by using typhoid vaccine and rather rapidly increasing the dose, chills can be produced at required intervals extending over a period of several weeks Dr George Hall has fever curves from typhoid *injections* that compare favorably with those following malaria and the results should be equally favorable The fever of malaria is of protein origin, caused by the escape of protein into the circulation as the parasite leaves the red blood corpuscle The typhoid vaccine has distinct advantage over that of malaria, as the patients do not become anemic, and the interval *between chills can be regulated*

The number of recoveries reported from malarial treatment varies from 30 to 40 per cent, that is, patients who are able to return to their previous occupations

Multiple sclerosis is another disease in which protein therapy is being used extensively There is a difference of opinion with regard to the infectious character of this disease The improvement reported following this form of therapy speaks for its bacterial origin Recently Kathleen Chevassut, working in the Westminster Hospital, obtained a filtrable virus from the spinal fluid in 176 out of a total of 186 cases

Gerstmann, a student of Wagner-Jauregg s, treated one series of patients with malaria another with typhoid vaccine The typhoid series included twenty-nine patients of the chronic progressive type, none of whom had shown any tendency to remissions Twenty-seven per cent of this group showed marked improvement Forty-two patients were treated by inoculation with malaria In the recent acute forms marked improvement was noted in 26 per cent and moderate improvement in 46 per cent In the chronic progressive type, 16 6 per cent were definitely improved After the treatment was discontinued, the improvement was progressive and up to the time the report was made there was no relapse

Dreyfus and Hanau treated two series, one with typhoid, *the other with malaria In the* typhoid series of ten cases, each patient received twenty injections of typhoid vaccine Seven of these patients were of the chronic progressive type Two of this series were definitely improved, with no tendency to relapse after a period of seven months The patients with a history of remissions were all much improved One was able *to return to her previous* occupation of modeler In the series treated with malaria, ten were of the chronic progressive type Two of these were greatly benefited and nine definitely improved All of the patients had been under observation from one to five years and had never had a spontaneous remission

This new field for nonspecific therapy deserves continued *trial* If the treatment is begun early, before irreparable tissue changes have taken place, complete recovery may be possible It is too early to predict the permanence of the improvement It is possible that other chronic neurologic diseases may be amenable to this form of treatment

CHEMOTHERAPY

Dale[1] defines chemotherapy as the specific treatment of infection by artificial remedies If we accept this definition, chemotherapy had its beginning centuries ago The discovery of all our older specific drugs was the fruit of prolonged experimentation Uncivilized peoples apparently believed that the vegetable kingdom held curative remedies Repeated trials, and, finally, an observation that a decoction from a certain herb or tree favorably affected the disorder, probably explains the discovery of ipecac, quinine and chaulmoogra oil

Ehrlich s conception of chemotherapy was the production by synthetic chemistry of substances that were toxic for the parasite but harmless to the cells of the host We are all familiar with the success of his efforts in producing substances capable of destroying the parasite invaders There is a growing belief, however, that the method of action of these substances was not by directly destroying the parasite No one questions his results, but doubt is cast on his hypothesis

H H Dale, the English pharmacologist, has been a leader in questioning this hypothesis He has many disciples who believe with him that these agents are not directly parasiticidal but act as cellular stimulants resulting in the production of something that destroys the invader, thus somewhat resembling protein therapy in action

Dale and Dobell[2] studied the effect of emetine on *Endameba histolytica,* the recognized cause of amebic dysentery It is difficult to picture the destruction of these parasites by any direct action following the hypodermic injection of eight or ten small doses of emetine They were able to demonstrate that some strains of *Endameba histolytica* were not killed in vitro by a

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[1] Dale H H *Physiol Rev* 3 359 (July) 1923

[2] Dale H H and Dobell C J Pharmacol & Exper Therap 10 399 (Dec) 1917

1:1,000 solution of emetine, although able to live several hours they would not multiply. In weaker dilutions (1:5,000 or 1:10,000) the ameba would survive several hours. Methyl psychotrine, another alkaloid of ipecac, is much more toxic to the ameba in vitro but is not of value in the treatment of amebic dysentery. The harmless *Endameba coli* and *nana* are not destroyed by any of the alkaloids of ipecac. Dale calls attention to the fact that *Endameba histolytica* is the only one of these that invades and multiplies in the tissue of the host, and suggests that this might indicate that emetine acts on the host with prevention of tissue invasions. As other investigators have failed to confirm Dobell's results, the experiments have been repeated.[3] In their first experiments they used a medium containing coagulated egg albumin. In this medium the emetine disappeared after incubation, apparently, it entered the solid egg albumin. In a medium of horse serum and Ringer's solution, the amebas were destroyed after four days' incubation in a dilution of 1:750,000. They found that the p_H of the medium had a decided effect on its amebicidal activity—an acid environment lessening the activity of the emetine.

With the marked tendency for the emetine to become inactive in the presence of coagulated albumin, it is a question how much of it reaches the large bowel in an active state. As its activity is modified by so many factors, it is safe to say that, up to the present time there is no satisfactory evidence that its therapeutic activity is due to its direct amebicidal action.

Extract of chaparro amargoso has no effect on *Endameba histolytica* in vitro but is of decided value in the treatment of the disease. Acetarsone (stovarsol) is only mildly amebacidal in vitro but destroys the ameba in the host.

Malaria.—Quinine added in vitro to blood containing the plasmodia fails to support the view that its action is directly parasiticidal. It is quite certain that the amount of quinine in the blood after the usual dosage will not directly destroy the plasmodia. Several hypotheses have been evolved to explain its mode of action. Morgenroth evolved the conception that the quinine is fixed to the red blood corpuscle, acting by destroying the parasite within or by blocking its entrance into the corpuscle, thus interfering with the asexual cycle. Morgenroth's view that quinine has an affinity for the corpuscle has not been verified. The method of action of quinine has not been determined. If its direct action can be ruled out, it becomes necessary to introduce the host as an important factor in the destruction of the plasmodium.

Mercury.—When a gumma is seen to disappear after a fortnight's treatment with one-fourth grain (16 mg.) of yellow mercurous iodide three times a day, it would require an imaginative mind to believe that, even if the mercury were converted in the body into mercuric chloride, this small amount could destroy *Spirochaeta pallida*.

Arsenicals.—Trypanosomes and *Spirochaeta pallida* respond in much the same manner to arsenic and to bismuth. The dyes, however, act only on the trypanosomes. Neoarsphenamine is very slightly spirocheticidal in vitro. The spirochetes will live in dilutions of 1:5000 and when transferred to a fresh culture medium will grow in a normal manner. A 70 Kg. man receiving 0.5 Gm. of this drug would have a blood concentration of less than 1:10,000. This dilution would quickly weaken, as the arsenic is rapidly excreted through the kidney. Ehrlich attempted to explain the action of arsphenamine by its conversion in the body to the highly spirocheticidal arsenoxide. It has not been determined that this chemical reaction takes place. If it were definitely established, it would mean that the host was playing a role in activating the drug.

Levaditi claims that atoxyl has little effect in vitro on the trypanosomes. If, however, he made an extract of fresh liver, added atoxyl to it and incubated the mixture for three hours, it became highly trypanocidal. He believes that the arsenic enters into combination with tissue albumins, resulting in the formation of a toxalbumin that is parasiticidal. Uhlenhuth takes the view that the arsenic stimulates the host cells to liberate an antibody-like substance.

Bismuth is a valuable remedy in syphilis. No salt of bismuth is more than mildly parasiticidal. If we accept Ehrlich's hypothesis of the conversion of arsphenamine into the parasiticidal arsenoxide, another explanation would be required to explain the action of bismuth. It is highly probable that eventually it will be shown that the mode of action of these two chemicals is alike. Levaditi found that liver extract from different species would activate the arsenic, but to a different degree. Different organs in the same animal possess this quality in varying degrees. The liver of the guinea-pig was less active than the liver of fowls or of rats. The whole blood, blood serum, red corpuscles or leukocytes were inactive, as were egg and yeast.

This varying activating power of organs might explain the selective action of drugs. Tryparsamide, which is of value only in syphilis of the central nervous system and especially in dementia paralytica, might be activated only by brain tissue. In the late stages of trypanosomiasis, i. e., when the organism has invaded the central nervous system, atoxyl is useless, although it is valuable in the earlier stages of this disease. Tryparsamide, however, will destroy the trypanosomes in the central nervous system, at least in a considerable number of patients.

Bismuth.—Levaditi,[4] who introduced bismuth in the treatment of syphilis, repeated the experiment he had made with atoxyl using *Spirochaeta gallinarum*. None of the salts or the pure metal have more than a weak action on spirochetes in vitro. When an animal was given bismuth intravenously and blood was withdrawn at four-hour intervals, the serum was not spirocheticidal. When mixed with cell free liver extract and incubated for a few hours, it become highly spirocheticidal. This suggests that some cell constituent played a role in the activation. He found finely powdered metallic bismuth more efficient than any of the salts. Only a fraction of a milligram of bismuth was required to activate 5 cc. of liver extract. He believes that bismuth unites with the tissue extract to form a complex colloidal bismuth which he names bismoxyl.

This active substance will pass through a porcelain filter but is nondialyzable and is destroyed by a temperature of from 80 to 100 C. Liver placed in boiling water for five minutes still retains this property to a high degree. Prolonged boiling renders the liver inactive. It is resistant to dessication retaining its activity without notable change when kept at laboratory temperature for 125 days.

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[3] Laidlaw, P. P.; Dobell, C., and Bishop, A.: Parasitology 20: 207 (July) 1928.

[4] Levaditi, Constantin: Le bismuth dans la traitement de la syphilis, Masson et Cie, Paris, 1924.

S Lumholt has shown that in animals, following the injection of bismuth, the blood serum enters into combination with the bismuth It is bound so firmly to the serum that it cannot be separated by washing The purpose of this union is not known, but apparently it has something to do with its spirocheticidal activity

The arsenicals, if given in doses too small to destroy the trypanosomes, lead to the development of resistant strains which cannot be destroyed by larger doses of the drug When such a resistance has been developed in a mouse, and the trypanosomes are transferred to a rat, the resistance disappears Such a strain, after forty passages through rats, will regain its resistance immediately if transferred to a mouse Apparently, the host or species of animal must play the primary role in creating this resistance If one wished to speculate, one might say that the parasite had acquired a resistance to the hypothetic combination of arsenic and mouse protein but was not resistant to the combination of arsenic with rat protein

Not only does Bayer 205, a naphthylamine-sulphonic acid of undeclared composition used in the treatment of trypanosomiasis, destroy the parasite, but following this the animal is immune to reinfection for several weeks or even two or three months In vitro, even in a concentration of 1 100, from twenty-four to forty-eight hours is required to immobilize the trypanosomes A dose of 50 mg per kilogram will sterilize the blood of an infected animal in sixteen hours In order to accomplish this, the drug must either be changed in the body to render it more trypanocidal or it acts on the cells of the host, resulting in the formation of an immunizing substance

Very small amounts of Bayer 205 will protect animals from infection This is presumptive evidence that it acts as a cellular stimulant

Reference has already been made to the immunity of weeks or months after treatment with Bayer 205 During this period the serum of the animal or extracts from its organs possess curative properties This might be accounted for by the possibility of the drug being retained in the tissues It is more probable, however, that the tissue of the host is responsible for this immune substance

There is other evidence that the host plays an important role in the activity of Bayer 205 This drug will destroy the trypanosomes in one species of animal, while a different species infected with the same trypanosome may be resistant to it Trypanosomes are easily destroyed in the mouse but are affected little if at all in the horse and ox The apparently harmless natural infection of wild rats with the trypanosomes is likewise not affected by Bayer 205

Trypan red will destroy the trypanosomes in the mouse but is useless in rats infected with the same strain

With the development of chemotherapy by Ehrlich, it was believed that a method had been evolved for the scientific study of specific drugs Ehrlich and his followers succeeded in making arsenical compounds which were of great value in the treatment of syphilis and trypanosomiasis He also produced dyes that are effective in trypanosomiasis and other protozoal tropical diseases No one questions the value of these agents, but perhaps here as has happened many times before, a valuable discovery was made by following a wrong hypothesis

122 South Michigan Avenue.

STUDIES OF FEMALE GENITAL HYPOPLASIA

I A PRELIMINARY SURVEY OF THE PROBLEMS INVOLVED *

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Hypoplasia of the female reproductive organs is a common condition, as every gynecologist can attest Its incidence has never been exactly determined In a consecutive series of fifty unmarried adult women, some degree of hypoplasia was observed five times Of 100 wives whose marriages were sterile, 42 were demonstrably hypoplastic Among parous women, on the other hand, the condition is seldom seen

The chief importance of genital hypoplasia lies in the subnormal fertility which it necessarily induces Present in about 40 per cent of sterile matings, it probably assumes major proportions in the causation of at least half that number, if so, hypoplasia may be considered a definite barrier to fertility in some 400 000 American marriages When conception does occur miscarriage is common, and in cases going to term uterine inertia and postpartum atony are often encountered Other symptoms are dysmenorrhea and amenorrhea, and at times excessive flowing

In spite of the frequency of hypoplasia and its obvious importance, it has engaged the interest of the medical profession hardly at all The subject receives only casual mention in the textbooks and the current literature on it is almost nothing Physicians appear ready enough to make, rightly or wrongly, a diagnosis of 'infantile" uterus, present-day treatment, however, is worthless as applied to the established adult case, while the important opportunity of applying preventive treatment in the adolescent case is altogether neglected

About a year ago my co-workers and I came to feel that, in view of the facts just stated, a systematic investigation of pelvic hypoplasia might be productive of useful results There are numerous possible lines of approach, all of which tend to converge on certain definite problems Disregarding the question of incidence as mainly of academic interest, we have for consideration five problems of practical importance These are etiology, diagnosis and curative treatment of established hypoplasia in adult women, and recognition and prophylactic treatment of threatened or incipient hypoplasia in adolescent girls

ETIOLOGY OF GENITAL HYPOPLASIA

We are at present in no position to make dogmatic statements about the causation of these developmental arrests Nevertheless, a reasonable basis for opinion is afforded by certain established facts

There is an abundance of evidence, both clinical and experimental, to indicate that growth and development are under the immediate control of the endocrine glands Severe endocrine failure in childhood leads to conspicuous retardations, of which cretinism and dystrophia adiposogenitalis are well defined examples In these extreme instances the hypoplasia is general as well as genital In cases of milder endocrine failure the developmental deficiency may be limited to the

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* This paper is the first of a series of reports on an investigation undertaken by the Boston University Commission on Sterility The studies are being conducted by the Department of Gynecology of the Boston University School of Medicine with the collaboration of the Evans Memorial for Clinical Research and Preventive Medicine

genital organs An endocrinopathy that occurs just before or during the adolescent years seems likely to have this limited effect, since the reproductive system is the only part of the body which is normally undergoing active differential development at that epoch

The foregoing ideas are further supported by the fact that the direct study of girls with delayed menarche commonly gives objective evidence of an endocrine malfunction Thyroid failure is sometimes encountered, but in the great majority of such cases the endocrinopathy is an insufficiency of the anterior lobe of the pituitary This observation is entirely in keeping with recent studies of the physiology of the pituitary, which ascribe to that gland the role of activator or motor of the ovary In hypoplasia the ovary itself is never primarily at fault

In studying a group of delayed adolescents, one is also impressed with the relatively high incidence of non-endocrine conditions of a generally debilitating character Among these are focal infections, congenital syphilis, rickets, anemia diseases of the central nervous system, unbalanced nutrition and faults of hygiene It seems that such influences contribute to developmental retardation Whether they do so directly, or indirectly by inducing an endocrine depression, is a question

DIAGNOSIS OF HYPOPLASIA IN ADULTS

In the histories of adult women whose genital organs are hypoplastic, two items are prominent—menstrual disorders and low fertility Such symptoms are, however, far from pathognomonic, they may be absent in hypoplasia and are frequently present in normally developed women as the result of other conditions The most significant detail of the history appears to be any derangement of the menstrual function during adolescence, and in particular delayed onset

General physical examination often fails to show evidence of retardation, indeed, many women in this group are strikingly well developed as regards their general status In a fair number, however, there are obvious stigmas of an earlier inadequacy, such as a disproportion between the trunk length and the limb length, a masculine distribution of hair, and a tendency toward middle third or generalized obesity

Metabolic tests and other vital function evaluations usually show little or no deviation from the normal We believe that most of these patients suffer a phase of endocrine insufficiency during the critical period of adolescence In the majority of cases the phase is transient only, and a normal glandular balance is soon reestablished Thus the adult woman may give no evidence of persisting endocrine malfunction, although there is a permanent residuum of the old disturbance in the form of imperfectly developed genital organs

Local examination reveals characteristic stigmas in almost every case The vulva is sometimes hypoplastic but more commonly normal The ovaries often contain follicular cysts, since the oogenetic function is defective, in the more extreme cases the ovaries may be of the elongated and lobulated fetal type The tubes are not unlikely to present a congenital impermeability It is in the uterus, however that one encounters those signs which are at the same time most distinctive and most accessible to the examiner The organ as a whole tends to be slightly below normal size The postion of the corpus is variable, the long and conical cervix is anteflexed because of the shortness of its anterior attachments, the so-called Goffe's fascia

The constant anatomic feature of the hypoplastic state is relative length of the cervix and relative shortness of the uterine body The cervix constitutes about two thirds of the infantile uterus and only one third of the normal adult organ In hypoplasia the proportions range between these extremes I described a uterine index[1] which expresses the ratio of corpus to cervix Measurements are taken in the living patient with a modified uterine sound, we also have observations on autopsy material Representing the length of the entire uterocervical cavity by U and that of the cervical canal by C, the index is calculated according to the formula $\frac{1}{2}\left(\frac{U-C}{C}\right)$ The resulting figure is 0 25 for infantile and 0 75 for normal adult uteri Intermediate figures represent the various degrees of hypoplasia, which can thus be quantitatively evaluated

TREATMENT OF HYPOPLASIA IN ADULTS

From time to time there have been desultory attempts to treat established hypoplasia in the adult woman The methods employed fall into two groups, local and constitutional

Local methods have included electricity, heat, massage, dilation and packing All such assaults on the hypoplastic uterus are obviously futile, for they do not influence the associated hypoplasia of the ovaries, which is the really important item in the picture Surgery may eliminate the secondary results of subnormal function, particularly inspissation of the endocervical mucus and formation of follicular cysts in the ovaries, but is powerless to correct the hypoplasia which primarily occasions functional subnormality

Constitutional treatment in recent years has consisted mainly of endocrine medication Two reasons are apparent for the uniform failure of this type of therapy The first is that the exhibition of glandular products in ordinary practice is more or less haphazard, the patients often receiving preparations that are nonspecific, inadequate or inert Another and a more fundamental reason lies in the disappearance of the growth impulse at the close of the adolescent period If the developmental urge is dead, neither by taking thought nor by giving glands can one reasonably expect to add a cubit to the stature

Although at present no method is known whereby hypoplastic organs in the adult patient can be stimulated to complete their development, the problem should not be abandoned as hopeless In some few cases, at least, the growth impulse appears to be dormant rather than dead for many years after adolescence It is sometimes reawakened by the stimulus of a normal sex life, and always by the influence of a pregnancy The mechanism of such phenomena requires to be studied with a view to discovering how the results can be duplicated Possibly a better understanding of pituitary function will provide the means either of evoking directly a postpubertal phase of pelvic development, or else of promoting oogenesis so that pregnancy with its favorable effect may become relatively frequent in hypoplastic cases

DIAGNOSIS OF HYPOPLASIA IN ADOLESCENTS

Incipient or threatened hypoplasia in adolescent girls must be diagnosed by indirection We believe that the diagnosis is strongly suggested, and is for practical purposes to be made, if the patient exhibits a combination of two items—abnormal menstrual behavior, and demonstrable constitutional depression

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[1] Meaker S R A Uterine Index of Development The Definition of a New Diagnostic Sign Boston M & S J **196**: 615 616 (April 14) 1927

The relation between conpubertal menstrual disturbance and incipient genital hypoplasia is not yet conclusively demonstrated but is probable beyond any reasonable doubt There is justification in assuming that an immature uterus and semidormant ovaries are unlikely to function normally In adolescent girls, however, abnormalities of the menstrual function are commonly associated with constitutional disturbances

With reference to the present problem, any type of conpubertal menstrual abnormality is worthy of attention Dysmenorrhea is probably of least significance Irregular interval scanty flow, and secondary amenorrhea are obviously indicative of functional inadequacy Puberty bleeding usually suggests imperfect oogenesis The most important type of menstrual disturbance is, in our opinion, delayed menarche The onset of menstruation occurs before the fifteenth birthday in about 80 per cent of American girls, and before the sixteenth in 88 per cent Many of the residual 20 per cent, and most of the residual 12 per cent, can be demonstrated to have constitutional disabilities capable of retarding development

Menstrual misbehavior is nearly always the symptom that first draws attention to the need for thorough investigation of these cases The necessary study then comprises history and general physical examination, and laboratory tests designed to evaluate the vital functional level from the endocrine point of view

Local pelvic examination is generally uninformative in the adolescent case so far as hypoplasia is concerned Its main value would lie in ruling out such rare conditions as pseudohermaphroditism and imperforate hymen, and in the occasional identification of some incidental abnormality Everything considered, the most practical plan appears to be the omission of all routine local examinations In a few selected cases, inspection of the vulva or recto-abdominal palpation may be considered advisable

TREATMENT OF HYPOPLASIA IN ADOLESCENTS

If the foregoing views about the causation of genital hypoplasia are correct, and if our methods of investigation are adequate the necessary lines of treatment will be self-evident Both nonendocrine and endocrine abnormalities require to be corrected

A fault commonly encountered, even among well-to-do patients, is unbalanced nutrition, especially an inadequate protein intake The general hygiene of the modern girl leaves much to be desired Milder grades of anemia are frequent and appear to have a particular depressing effect on the reproductive system Chronic focal infection contributes demonstrably to disturbance of the endocrine functions In occasional cases congenital syphilis, rickets, lesions of the central nervous system and other disease entities require treatment on the ground of their harmful influence on the metabolic level, as well as on their own merits

The mechanism of endocrine treatment in the adolescent patient is primarily substitution, with an excellent chance of secondary homostimulation Monoglandular therapy gives better results than pluriglandular if the primary focus of failure is normalized, responsive disturbances in other glands tend to regulate themselves The gland required is usually the anterior lobe of the pituitary, occasionally the thyroid, and never the ovary Success depends on the use of potent preparations in adequate dosage

SUMMARY

This preliminary paper contains too much speculative material to warrant any conclusions It is hoped that subsequent papers will embody conclusions of a definite and practical character The main points of my present thesis may be summarized as follows

1 Female genital hypoplasia is a common condition and a major factor in the causation of sterility

2 The immediate cause of such hypoplasia is most commonly a conpubertal insufficiency of the anterior lobe of the pituitary

3 The diagnosis of established hypoplasia in adult women depends mainly on pelvic examination and the recognition of characteristic stigmas in the uterus

4 Treatment of established genital hypoplasia is at the present time wholly ineffectual

5 The diagnosis of incipient or threatened hypoplasia in adolescent girls depends, first, on the recognition of abnormal menstrual behavior, and, secondly, on the identification of depressing constitutional factors, both endocrine and nonendocrine

6 The treatment of incipient or threatened hypoplasia consists in the elimination of all depressing constitutional factors, and is a hopeful undertaking

7 In the management of the adolescent cases there exists a new and important opportunity for the practice of preventive gynecology

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XEROSTOMIA *

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Case 1—April 15 1919 there appeared at my office a woman, aged 34, complaining of excessive dryness of the mouth for the past eight years For the past year there had been a discharge of pus from the mouth of Stenson's duct on the left and the same purulent discharge was now beginning from the duct on the right There was no saliva or mucus and deglutition could only be accomplished when the food was moistened with gulps of water, milk or coffee There was no perspiration even on exertion in extreme heat

Examination of the nose showed practically normal nasal fossae, with no suggestion of atrophy but with little or no secretion The mouth was extremely dry with flocculent masses, resembling inspissated mucus, adhering to the mucosa throughout The tongue was dry, cracked and somewhat inflamed The nasopharynx was free The teeth were in exceedingly poor condition in spite of excellent care, and were soft and crumbling Pressure along each cheek from the parotid toward the opening of Stenson's duct brought forth a minute droplet of pus Pus could also be recovered on placing a glass suction tube over the mouth of the duct A probe introduced into the duct failed to elicit the presence of a stone Treatment such as suction, potassium iodide and local applications failed to give any relief The patient was seen several times for about a month when she was lost sight of

She was seen again in July, 1920 when she gave a history of abscesses in various parts of the body which had responded finally to vaccines There was apparently less discharge of pus from the parotids She appeared again in May 1921 when she gave a history of discharge of pus from the sublingual glands also Her condition otherwise was about the same except that her teeth were in worse condition

She was not seen again until May, 1929 when she reappeared complaining of fulness and some deafness in the right ear for the past month Examination showed considerable retraction of the right tympanic membrane with

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* Read before the American Laryngological Rhinological & Otological Society Atlantic City N J May 29 1930

probably some effusion The membrane on the left showed some thickening and retraction The hearing distance for conversational voice was 1 meter on the right and 4 meters on the left, increasing to 5 meters on the right and 6 meters on the left following inflation by the Politzer method The condition in the mouth was about the same as on the previous examinations, except that most of the teeth were gone and replaced by a plate She has been seen at intervals since At the recent examination the following history was elicited This has been written for me by the patient herself in such a concise manner that I shall give it in her own words

As a child I was never considered very robust and was very peculiar in my habits of eating I lived, in fact, on starches and sweets" She told me that she could remember her mother preparing half a dozen different kinds of food, all of which she would refuse to eat She ate no fruits meats, green vegetables or butter and drank no milk Her diet consisted of potatoes, starchy foods, pastries and bread, coated with jam instead of butter

To return to her narrative

"I had the usual childhood diseases including diphtheria and scarlet fever, and a mild case of typhoid When about 20 I became afflicted with boils and carbuncles lasting for more than a year For years after that the slightest scratch would develop into an infection During 1909 1910 a serious stomach condition began which restricted my diet to a very few things At this time my own physician was abroad and the other physicians whom I consulted diagnosed the condition as acute indigestion and gastritis In May, 1910 I was operated on for appendicitis A minor abdominal operation was also performed Before leaving the hospital I noticed that my mouth was rather dry A few months later all my teeth began to ache and became so sensitive that I could scarcely eat. Dentists told me that it must be a nerve condition, as there were no cavities The aching became so intense that I was forced to have nearly all the nerves removed under general anesthesia This stopped the pain but the teeth began to crumble and break until I had over twenty crowns and bridges in my mouth The dryness kept increasing

In 1916 the salivary glands began to swell for two or three days at a time This swelling would be accompanied by chills and fever This condition had occurred about every four weeks for four or five years, when I discovered that on pressing on the glands quantities of pus would be discharged At times, vaccine treatment seemed to help During most of this time my stomach was in such a condition that I had to be very careful of my diet It was finally decided that there must be an ulcerated condition, which was relieved by frequent pumpings and washings

'In 1921 after a severe case of influenza my eyes became infected For weeks they were as red as raw meat and were full of pus Then I found that I had no tears The sight in the left eye was only 14 per cent.

'At this time I wrote to Dr McCollum of Johns Hopkins describing the condition of my mouth and eyes and giving him a history of my peculiar habits of eating when a child, as well as my restricted diet during my years of stomach trouble I had eaten scarcely any foods containing fats and had used no cream milk or butter to speak of He immediately wrote me giving me a very explicit diet to follow This consisted of orange juice tomatoes cooked greens of all kinds and raw vegetables together with plenty of milk, cream and butter, whole wheat bread and some meat In addition I was to take cod liver oil and calcium. The milk I was unable to digest, but I could take the cream butter and cod liver oil In six weeks the sight of my left eye was doubled and the inflammation had disappeared

A year later I saw Dr McCollum in Cleveland He was delighted with the change in my eyes The mouth condition however remained the same After several attacks of neuritis and arthritis all but seven of my teeth were extracted The discharge of pus from the salivary glands still continued In March, 1929 I was again in the hospital with some sort of general poisoning resulting in arthritis

In addition to the case described I will report briefly three other cases of xerostomia, two from the records of Lakeside Hospital in the service of Dr M A Blankenhorn and one from a personal communication from Dr Frank J Geib In none of these cases is there a history of a deficiency diet In fact, the etiologic factor in most of the reported cases is decidedly indefinite, so that I am merely suggesting a deficiency diet as a possible etiologic factor

Case 2—A woman aged 54 complained of general weakness and a history of dry mouth for the past four months There was a history of glycosuria easily controlled by diet The mouth was exceedingly dry with discharge of pus from Stenson s duct. This pus showed some epithelial cells and a few small diplococci The patient herself attributed the dryness of the mouth to the taking of some medicine, the nature of which she did not know The nasal mucosa was dry and atrophic

Case 3—A woman aged 56 also complained of general weakness and dry mouth for the past four years There was no perspiration even in the warmest weather" She said that her mouth was so dry that she could not lick a postage stamp Pus from the sublingual glands showed a large number of white blood cells and a few diplococci There was no saliva on stimulation with the faradic current but some sweating on administration of pilocarpine The general examination was negative

Case 4—Dr Geib s patient, a single woman, aged 56, seen in 1924 complained of dry mouth for one year, the condition immediately following the death of a brother to whom she was much attached There was some deficiency in tears and a marked falling out of her hair Sweating was present only on rare occasions Pus could be expelled from Stenson s duct but none from the submaxillary or sublinguinal glands Three years later the condition was still the same and she complained also of a marked dryness of the eyes The teeth were also bad There was no relief from treatment

Xerostomia was first reported by Sir Jonathan Hutchinson[1] in 1888 At that time he reported one case and suggested the name for the disease Hadden[2] reported a case in 1889 and Hutchinson[3] a second one later In 1922 only 47 cases were reported in the literature Of these no etiologic factor could be found in 23 Of the remainder, 3 followed influenza and 7 were due to psychic disturbances, 3 to a sudden loss of teeth, 2 to a swelling of the glands, 1 each to a nervous disorder, to mumps, to a blow on the head, to pregnancy, to a heavy meal, to bad care of the mouth and caries and 2 to stone

Curschmann[4] attributes the origin of xerostomia to (1) senile atrophy, (2) psychic influences and (3) disease in the medulla, where the centers are located

Schmidhuber[5] considers most cases of idiopathic origin but mentions as causative factors (1) injury through stone (2) a possible central nervous origin, and (3) a combination of the two causes, the stone being a probable result of the nerve involvement

The psychic origin, a severe and sudden emotion, in one of Hutchinson s cases was most striking Ninety per cent of the reported cases were in women and practically all the patients were past middle age

In none of the reported cases has a deficiency diet been mentioned as an etiologic factor In my case it certainly antedated the condition described Whether the evident infection of the parotid preceded the atrophy and was therefore a causative factor, or whether it was an ascending one from the multitudinous flora of the mouth and gained access to the gland more readily on account of the absence of a descending current of saliva, it would be difficult to say The latter would seem to be the more probable hypothesis since, in the absence of a current of saliva through Stenson's duct, bacteria could easily gain entrance to the gland itself

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[1] Hutchinson Jonathan A Case of Dry Mouth Tr Clin Soc. London **21** 180 1887 1888

[2] Hadden Xerostomia (Dry Mouth) Brain **11** 484-486 1888-1889

[3] Hutchinson Jonathan A Second Report on Xerostomia or Dry Mouth with an Additional Case Tr Clin Soc London **22** 25 1888-1889

[4] Curschmann Hans Ueber Xerostomie Arch f Verdauungskr **18** 211 1912 Munchen. med. Wchnschr **76** 269 (Feb 15) 1929

Schmidhuber K F Ein Beitrag zur Klinik Xerostomie Munchen med. Wchnschr **69** 1406 (Sept.) 1922

In the foregoing report a deficiency diet as an etiologic factor is merely suggested as a possibility in this fairly rare and obscure disease

Osborn Building

GONORRHEAL SPURS A MISNOMER *

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One hundred consecutive cases of exostosis of the os calcis at the Mayo Clinic were reviewed with the purpose of ascertaining how frequently the gonococcus is a factor in the etiology of the disease

It is generally believed that exostosis of the os calcis is of gonorrheal origin This idea may have originated from a report by Baer,[1] in 1905, in which he recorded five cases of painful heels due to exostosis of the os calcis, and all of the patients gave a definite history of having had gonorrhea In two of the cases in which the spine was also affected, gonococci were found in the growths removed from the heels In another case three cultures were made at the time of operation, and, although the cultures were negative, they showed diplococci that were decolorized by Gram's stain

Waechter and Sonnenschein,[2] Murphy [3] and Epstein [4] recognized gonorrhea as the cause of some, but not all, cases of calcaneal spur Meisenbach [5] expressed the belief that trauma was the main cause Swett and Stoll [6] found calcaneal spurs in nine cases of hereditary syphilis In Merritt's [7] three cases and in Moorhead's [8] one case gonorrhea was the only known cause

Stiell,[9] in 1922, stated that about 90 per cent of painful heels are traumatic in origin, gonococcal inflammation of the plantar fascia being an infrequent cause of pain in the anterior portion of the ball of the heel where the plantar fascia gains attachment to the os calcis This condition has been termed "young man's gout", he cautioned physicians not to tell young men that all painful heels are due to gonorrhea

That the presence of calcaneal spurs is not always accompanied by painful symptoms was shown by Blenke,[10] who studied the feet of 600 normal persons and found symptomless spurs in 2 8 per cent Murphy stated that from 2 to 9 per cent of all normal persons past the age of puberty have symptomless calcaneal spurs In 6 per cent of our own series of cases with spurs there was no pain In our cases the youngest patients were aged 17 years and the oldest 75 Fifty-five per cent of the patients were between the ages of 25 and 44 years, and 16 per cent were aged more than 60 years

There were eighty-five men and fifteen women About 73 per cent of the women were aged 50 years or more

Calcaneal spurs are most common in persons who do most of their work standing, hence it is most commonly seen in barbers, dentists, motormen and conductors of street cars, policemen, store clerks, and persons in similar occupations The pain was directed to the heels in 55 per cent of the cases and to the feet in 39 per cent of the cases

In 44 per cent of the cases a history of gonorrhea was obtained In 5 per cent the heel became painful from three to four days after the onset of the gonorrheal symptoms, in 5 per cent after one to three months, in 56 per cent on an average of fourteen years, and in 3 per cent after thirty-four years In 40 8 per cent of these cases definitely septic tonsils were found, in 59 per cent infected teeth, and in 22 7 per cent definite prostatitis Pyuria was found in three cases only Roentgenograms showed 61 per cent bilateral spurs, 18 per cent in the left heel and 21 per cent in the right heel

In 56 per cent of the cases a history of gonorrhea was not obtained, and in this group 55 3 per cent of the patients had infected teeth, 20 per cent had septic tonsils, and 12 5 per cent had prostatitis Pyuria was found in six cases Roentgenograms disclosed 60 per cent of bilateral spurs in this group, 14 per cent on the left heel and 26 per cent on the right heel

Destructive arthritis elsewhere in the body was found in eight cases of patients without gonorrhea and in four cases of those with gonorrhea

A Wassermann test of the blood of eighty patients gave positive results in only three These three patients came to the clinic with other complaints, and calcaneal spurs were found during examination Antisyphilitic treatment was given to two of the three patients, and decided change in the condition of the calcaneal spur took place

We shall not consider treatment here except to mention the surgical results in sixteen cases in which operation was performed Thirteen of the patients were operated on at the clinic and three were operated on elsewhere Of the latter, one patient had a recurrence of the spur with symptoms, and the other two patients still complained of pain in the heel Of the former, ten reported excellent results from one to twenty years after operation

SUMMARY AND CONCLUSIONS

Forty-four of 100 consecutive patients with calcaneal spurs gave a history of gonorrhea, and of these 40 8 per cent had definitely infected tonsils, 59 per cent had infected teeth and 22 2 per cent had definite prostatitis Fifty-six patients did not give a history of gonorrhea, of these, 55 3 per cent had infected teeth, 20 per cent had infected tonsils, and 12 5 per cent had definite prostatitis Eight patients without gonorrhea and four patients with gonorrhea had ostearthritis of other joints Syphilis, so far as could be ascertained, was not an etiologic factor in any of the cases

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* From the Section on Urology the Mayo Clinic

[1] Baer W S Painful Heels Bull Johns Hopkins Hosp **16** 264 (July) 1905

[2] Waechter A L and Sonnenschein H D Painful Heels Due to Exostosis of the Os Calcis New York M J **102** 190 191 (July) 1915

[3] Murphy J B Painful Exostosis of the Os Calcis Surg Clin J B Murphy **4** 505 526 1915

[4] Epstein Sigmund On Focal Infection as a Cause of Painful Heel M Rec **96** 187 188 (Aug) 1919

[5] Meisenbach R O Pathogenesis of Spur Formation of the Os Calcis Am J Orthop Surg **9** 457-474 (Feb) 1912

[6] Swett P P and Stoll H F Hereditary Syphilis as an Etiological Factor in Spurs of the Os Calcis Surg Gynec Obst **22**: 674-678 (June) 1916

[7] Merritt E P Exostoses or Gonorrheal Spurs of the Os Calcis J A M A **69** 118 119 (July) 1917

[8] Moorhead E L Gonorrheal Spur on the Os Calcis Surg Clin Chicago **3** 623 626 1919

[9] Stiell W F Painful Heel Practitioner **108** 345 353 (May) 1922

[10] Blenke A Kalkanusporn Munchen med Wchnschr **1** 461 (April) 1917

A variety of etiologic factors for calcaneal spurs have been commented on by various observers Some factors, previously thought to be of primary importance do not seem to be significant in the etiology Neither syphilis nor gonorrhea is a gross factor in the etiology of most cases of calcaneal spurs Foci of infection in the teeth, tonsils or prostate gland, and possibly other obscure areas, particularly those bearing streptococci are probably a large factor in cases in which multiple etiologic factors are present The term "gonorrheal spurs" is a misnomer and should not be used

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THE SUPRARENAL CORTEX AND TUMOR *

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The possibility of a relationship between the suprarenal cortex and the growth of malignant neoplasms has recently become a prominent subject of inquiry Sokoloff[1] has recorded the absorption of transplanted animal tumors after they had been injected with a preparation of cortex and an iron salt through which the gland was assumed to direct metabolism Arloing, Josserand and Charachon[2] have described an inhibition of the growth of a mouse carcinoma after the subcutaneous introduction of suprarenal gland from a rabbit prepared by inoculations of the same tumor they[2] found a glycerinated extract equally effective whereas the normal gland proved to be inert whether extracted or not Activity was referred by these authors also to the cortex Coffey and Humber,[3] finally have said that an extract of suprarenal cortex from the sheep causes sloughing and ultimate disappearance of malignant tumors in man, but they regarded their investigation as still in the experimental stage and their results as decidedly inconclusive, though promising The critical reader will agree that the results are inconclusive but will be inclined to doubt their promise

My purpose in this paper is to describe briefly a repetition of the experiments of Arloing and his colleagues, a full account will appear later in the *Journal of Cancer Research*

Two standard mouse tumors were investigated—carcinoma 63 and sarcoma 180, the latter having been included merely for completeness, as the French authors specifically limit their conclusion to an epithelial growth Twenty-seven tumor-bearing mice were given suprarenal gland from rabbits previously treated with the strain of tumor which these mice bore while twenty-five others received suprarenal gland from normal rabbits The gland was administered in the form either of intact fragments or of a glycerin extract exactly according to the directions of Arloing and his associates

Although it had been planned to repeat their experiment on a rather large scale it was soon apparent that the treatment contained no promise of success and the work was accordingly abandoned No real inhibition of growth could be discovered, though it should not be forgotten that this statement applies only to the two neoplasms used Perhaps an occasional tumor such as that employed by the French investigators may be influenced, but any treatment so narrowly restricted as this would hardly be a fruitful subject of extended inquiry

CONCLUSION

The suprarenal glands of rabbits that have undergone preliminary treatment with carcinoma 63 or sarcoma 180 have no demonstrable inhibitory effect on the growth of these tumors in mice

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* From the Institute of Cancer Research Columbia University F C Wood Director

[1] Sokoloff Boris Suprarenal Cortex and Cancer J A M A **94**: 652 (March 1) 1930

[2] Arloing Fernand Josserand A and Charachon J Modifications evolutives de l épithelioma experimental de la souris blanche par greffes de surrenales provenant de lapins prepares avec ce meme epithelioma Compt. rend. Soc. de biol **100** 1035 (April 19) 1929 Modifications evolutives de l epithelioma expérimental de la souris blanche par injection d extraits glycerinés de surrenales provenant de lapins prepares avec ce meme epithelioma Compt. rend. Soc de biol **101** 1140 (Aug 13) 1929

[3] Coffey W B and Humber J D The Effect of a Suprarenal Extract for Malignant Growth J A M A **94** *359* (Feb 1) 1930 The Coffey Humber Treatment J A M A **94** 652 (March 1) 1930

PREGNANCY AND PARKINSONISM

REPORT OF A CASE *

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Numerous papers have appeared dealing with acute encephalitis complicating pregnancy since von Economo[1] first reported a series of cases of epidemic encephalitis in 1918 The combination of pregnancy and chronic encephalitis (parkinsonism) however, has received comparatively little attention by writers on this subject The present study of chronic encephalitis in pregnancy has been undertaken for this reason and in order to determine, if possible, the effect of chronic encephalitis on the gravid state and vice versa

It might be worth while to summarize the literature of acute encephalitis in pregnancy before proceeding with the discussion of chronic encephalitis or post-encephalitis parkinsonism in the gravid woman The suggestion that the pregnant individual is particularly susceptible to acute encephalitis has been advanced by students of small epidemics or of isolated cases, whereas those reporting large groups of patients observed no special predisposition associated with pregnancy Sternberg[2] reports that, of fourteen patients with acute encephalitis, five were pregnant, while the Glasgow investigation,[3] based on almost 400 cases, disclosed only a 0 5 per cent incidence The conclusion of Roques[4] that in any large epidemic only 2 or 3 per cent are pregnant women may be accepted, since it is founded on a most careful series of studies This author does not believe that the infection in pregnancy is of unusual severity, contrary to the assertions of Dimitz[5] and of Jorge[6] The latter authors, along with Robinson[7] and Bertolini,[8] assert that pregnancy aggravates the encephalitic symptoms Hall[9] supporting Roques, on the other hand, contends that there is no especial gravity attached to pregnancy as a complication of the condition

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* From the Department of Obstetrics Jefferson Medical College Hospital

[1] Von Economo C Wien klin Wchnschr **30** *581 585 1917*

[2] Sternberg C Wien klin Wchnschr **33** *785* 1920

[3] Chalmers A K Glasgow M J **104** 190 220 (April 4) 1925 Chalmers A K and MacGregor A S M Lancet **1** 610-612 (March 24) 1923

[4] Roques F Epidemic Encephalitis with Pregnancy Labor and the Puerperium Manchester Sherratt and Hughes p 139 Proc. Roy Soc Med. (Sect. Obst & Gynec.) **21** *1053 1062* (April) 1928 J Obst & Gynaec. Brit. Emp **35** 1 113 1928

[5] Dimitz L Wien. klin Wchnschr **33** 163 (Feb 19) 1920

[6] Jorge, R Paris med **11** 454-463 (June 4) 1921

[7] Robinson L Encephalite epidemique et gestation These de Paris 1921

[8] Bertolini G Folia Gynaec **19** 61 108 1920

[9] Hall A J Epidemic Encephalitis Bristol 1924

Clinically, acute encephalitis pursues the same course in the pregnant as in the nonpregnant patient, but the possibility of confusing the picture with other morbid complications of pregnancy must not be overlooked Atypical eclampsia and chorea may occasionally be regarded as encephalitis, as, for example, in the cases reported by Foulkrod[10] and by Commandeur[11]

Great variations in the death rate of acute encephalitis in pregnancy have been reported Robinson and Jorge allege that the mortality rate is 60 per cent while Roques holds that it is only 5 per cent Differences likewise are found with respect to the effects of labor on the course of the disease Pollastroni[12] and Hofer[13] believe that the natural evacuation of the uterus relieves the symptoms, while Benthin[14] and Jorge are certain that the stress of labor augments them The exhaustive investigation of the ministry of health[15] failed to uncover any relation between the act of labor and the severity of the nervous symptoms

The opposite aspect of the question, namely, the effect of acute encephalitis on pregnancy, requires mention Roques, in a review of the literature found that it was generally agreed that neither the labor nor the puerperium was affected by the concurrence of acute encephalitis He found however, no unanimity in regard to the influences of the disease on the course and outcome of gestation This author believes that it has no deleterious effect, but Jorge maintains that spontaneous abortion or premature labor is a common termination of pregnancy

Another interesting feature of the question is the possibility of the disease being transmitted to the fetus Cases, verified by necropsy, in which transmission seemingly occurred have been referred to by Marinesco[16] and by Santi[17]

The treatment of acute encephalitis in the pregnant does not differ from the management of the disease in ordinary patients It is the general belief that therapeutic abortion is not indicated, because of the lack of any proved relation between evacuation of the uterus and amelioration of the condition It may be stated that Hofer disagrees with this view and asserts that termination of gestation is invariably indicated in the presence of acute encephalitis Bompiani is more conservative, recommending intervention with pregnancy only in severe cases Until a better case for therapeutic abortion can be established, it seems unjustifiable to employ this procedure

CHRONIC ENCEPHALITIS IN PREGNANCY

Women who previously suffered attacks of epidemic encephalitis, with or without complicating parkinsonian symptoms, not infrequently become pregnant The influence of the pregnancy, labor and puerperium on the parkinsonism and vice versa is a problem as yet not entirely settled, probably because of the lack of reports of such cases and the divergence of the various observations A number of authors have reported more or less detailed descriptions of cases in which women partially or fully recovered from acute attacks and who later developed parkinsonism during a subsequent pregnancy, or conceived while in the parkinsonian state

Roques,[4] Hall,[9] Meyer,[18] Levy,[19] Garipuy,[20] Valente and David,[21] Somerville,[22] Offergeld,[23] Guillain and Gardin,[24] Critchley[25] and others have reported instances in which pregnancy occurred in women suffering from chronic encephalitis

Case histories of some of the foregoing authors are herewith briefly summarized Roques collected reports of forty cases of parkinsonism associated with pregnancy Of these, twenty-three had previously been reported by other authors, while Roques published seventeen for the first time Meyer reviews the history of a patient who made an apparently complete recovery One year afterward she became pregnant and lethargy recurred for two months In the sixth month of gestation, symptoms of paralysis agitans set in A normal child was born at term, but in the puerperium symptoms occurred, including bilateral ptosis, and dysphagia, which suggested a recrudescence of the disease

Levy records a similar case in which, two years after the attack with practically complete recovery, the patient, on becoming pregnant, developed a parkinsonian syndrome

Hall's patient suffered an acute attack in the third month of pregnancy, recovered and went to term, giving birth to a normal child Two years later she again became pregnant but noticed increasing difficulty in getting about Following the birth of this child the patient became worse and developed typical parkinsonism with extreme rigidity and slowness of movement Critchley briefly discusses the histories of seven patients with postencephalitis parkinsonism who subsequently became pregnant In every instance the patient continued to term, labor was normal and the infant healthy He could not satisfy himself as to any gross exacerbation of the neurologic state in any of the patients as a result of child bearing

These cases indicate the existence of several possible relationships between pregnancy and parkinsonism This aspect has not as yet received adequate consideration in the many papers dealing with this subject

For this reason, an effort has been made to answer the following questions bearing on such relationships 1 Is parkinsonism a more frequent sequel to acute epidemic encephalitis in pregnancy than to acute encephalitis in general? 2 What is the influence of parkinsonism on pregnancy, labor and the puerperium? 3 What is the effect of pregnancy on parkinsonism? 4 What is the effect of maternal parkinsonism on the child?

FREQUENCY OF PARKINSONISM AS A SEQUEL OF THE ACUTE DISEASE

The literature leads one to the conclusion that at least 75 per cent of the patients with acute encephalitis in pregnancy develop symptoms of paralysis agitans, whereas the incidence of the chronic state after ordinary acute encephalitis is not more than 25 per cent Roques reports an incidence of 80 per cent in his series of cases In the Sheffield epidemic of 1924, the sequela occurred in 77 per cent of the acute cases It therefore seems that women infected during pregnancy are more liable to develop parkinsonism than those acutely stricken in the nonpregnant state

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[10] Foulkrod C Am J Obst. & Gynec **5** 326 331 1923

[11] Commandeur and Eparvier Bull Soc. d obst. et de gynec. de Paris **19** 388-389 1920

[12] Pollastroni G Riv med **30** 17 19 1922

[13] Hofer C Zentralbl f Gynak **45** 1604-1607 1921

[14] Benthin W Zentralbl f Gynak **45**: 1604-1607 1921

[15] Ministry of Health (British) Eleventh report 1922

[16] Marinesco M G Bull Acad de med **37**: 1055 1061 1921

[17] Santi Rassegna d ostet e ginec. **29** 81 89 1920

[18] Meyer E Deutsche med Wchnschr **48** 341 1922

[19] Levy M G Manifestations tardives de l encephalite epidemique Paris 1922

[20] Garipuy R and Meriel Paul Gynec. et obst **18**: 2 5 (July) 1928

[21] Valente P and David M cited by Jorge Paris Med **11** 454-463 (June 4) 1921

[22] Somerville C W Tr Edinburgh Obst Soc. **48**: 127 130 192/ 1928.

[23] Offergeld D Arch f Gynak **133** 558 572 1928

[24] Guillain G and Gardin C Bull et mém Soc med d hop de Paris **45** 1417 1420 (Nov 4) 1921 abstr J A M A **77** 2151 (Dec. 31) 1921

[25] Critchley MacDonald Proc Roy Soc Med (Sect. Obst. & Gynec) **21** 1063 (April) 1928

In this connection it is interesting to note the time of onset of the encephalitis symptoms in the subsequent pregnancy Early onset seems to be the rule, Bompiani [26] and Fort [27] report the syndrome arising during the first three months of pregnancy Many authors have found cases in which parkinsonism dated from the delivery or shortly afterward Thus, Hall, Roques and Bompiani cite such cases and believe that the labor precipitated the chronic condition In nineteen of Roques' cases, women became pregnant after suffering from acute encephalitis In five cases, parkinsonian symptoms appeared for the first time during the early months of pregnancy, while in one case they appeared after delivery In nine cases, symptoms became more marked during pregnancy or in the puerperium Holmes [28] described a case in which the patient had acute encephalitis but never showed any sequelae She was delivered normally and within thirty minutes thereafter developed the typical clinical appearance of paralysis agitans Hall [9] and Strecker [29] describe cases in which parkinsonism developed in a later pregnancy, the acute attack having occurred during a previous gestation

INFLUENCE OF CHRONIC ENCEPHALITIS ON PREGNANCY

There is little evidence to indicate that parkinsonism exerts a deleterious effect on the course of gestation However, Stern [30] and Bompiani state that toxemia occurs more frequently in these cases than in the normal gravid woman Premature birth apparently is not more common in the parkinsonian patient, Roques reporting only six premature births among thirty-three cases of parkinsonism arising in pregnant women Offergeld, disagreeing with this view, claims that parkinsonism in pregnancy does not appear to render labor more difficult, since painless and easy labors have frequently been described in the literature This feature has been emphasized by Jorge, Del Sole,[31] Roques and Bompiani It may be said in summarizing the effect of parkinsonism on pregnancy that, notwithstanding certain adverse opinion, most observers believe that pregnancy is not more serious and labor not more difficult than in patients free from this complication

THE EFFECT OF PREGNANCY AND LABOR ON PARKINSONISM

Some authors (Hall, Roques and Offergeld) are of the opinion that pregnancy definitely aggravates paralysis agitans Del Sole cites three patients with parkinsonism who died of the disease after they became pregnant Pitimada [32] records the interesting history of a woman who became pregnant three times, the parkinsonian symptoms becoming aggravated on each occasion In 1927 Voron [33] reported a case of encephalitis unveiled by childbirth and confirmed by autopsy

In spite of these occasional cases, the possible deleterious effect of pregnancy on parkinsonism is not yet proved It must not be forgotten that the hundreds of victims of parkinsonism who have been safely delivered remain unreported, whereas the histories of outstanding cases of suddenly aggravated encephalitis usually are published

It cannot be denied, however, that some patients, at least, are made worse by gestation The question then arises, When is aggravation to be expected? It is generally agreed that the physical condition, if made worse at all, is likely to be impaired in the first half of pregnancy Roques found a total of thirty-four cases in which the parkinsonian syndrome had been aggravated during or made its first appearance in pregnancy In twenty-one cases, the onset or aggravation occurred early in gestation, in fourteen of these a second exacerbation was observed early in the puerperium The condition is also likely to be intensified during labor Hall and Del Sole report instances of this type The simplest explanation for this occurrence is, of course, that the stress of labor aggravates the disease, although the theory has been advanced that the fetus withdraws toxins from the mother, and, with the delivery of the child, this source of detoxication is unavailable However, little evidence has been cited in support of this hypothesis From a study of cases thus far reported, evidence is found to indicate that pregnancy has an unfavorable influence on parkinsonism, but the evidence is by no means conclusive

EFFECT OF PARKINSONISM ON THE CHILD

Actual cases of transmitted encephalitis are extremely rare Strecker has observed several children up to the fifth year of age without discovering any suggestion of abnormality Bompiani reported a case symptomatically resembling encephalitis in a child born of a mother afflicted with parkinsonism Unfortunately there was no autopsy protocol, but in general one may say that a full term child faces no stigma by virtue of having been born of a mother with encephalitis

REPORT OF CASE

Mrs M G, aged 31, white, a housewife admitted to the service of Dr P B Bland, June 10, 1929 had had her last period Sept 5 1928 and the estimated date of labor was June 15, 1929 The family record was irrelevant, disclosing no history of acute or chronic encephalitis nor could a history of chronic disease of the nervous system be obtained

Her past history was unimportant except for an attack of acute encephalitis She had measles whooping cough and smallpox in childhood She gave no history of having been operated on She was married in 1922 and gave birth to a healthy child in 1923 In 1925 she had an acute attack of encephalitis characterized by fever diplopia and somnolence Within a few months after the disappearance of the acute symptoms she began to notice some difficulty in gait and retardation in movement. Within a year she had a fully developed parkinsonian picture

She had a few slight labor pains June 10 Informed that she would soon be delivered, she sought admission to the hospital on that day At the time of admission her urine showed a faint trace of albumin and microscopically revealed a few leukocytes The specific gravity was 1 020 An examination of the blood yielded little of interest. The hemoglobin was 100 per cent the red cell count 4 190 000 the leukocyte count 7 800 The Wassermann and Kahn reactions were negative The blood chemistry showed sugar 107 mg and nonprotein nitrogen 23 mg A spinal tap was performed and the fluid was clear The spinal fluid was under normal pressure and the cytologic, chemical and serologic examinations were all negative

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[26] Bompiani R Policlinico **31** 1651 1654 1924 Riv d'ostet e ginec. prat **6** 104-114 1924

[27] Fort These de Lyon 1926

[28] Holmes Gordon Proc. Roy Soc Med (Sect Neurol) **20** 83 (Oct) 1927

[29] Strecker E. A and Willey G F Am. J Psychiat **4** 631-642 (April) 1925

[30] Stern F and Meyer Bisch R Wien klin. Wchnschr **31** 1922

[31] Del Sole E. Riv d'ostet e ginec. prat **6** 126-130 1924

[32] Pitimada F A Arch di ostet. e ginec **11** 124-141 1924

[33] Voron Dechaume and Malarte Bull Soc d'obst. et de gynec. de Paris **16** 66-68 1927

A neurologic examination made on the day of admission revealed a smooth, expressionless face, slow gait showing marche-a-petit-pas, general body rigidity, normal cranial nerves, and no signs of disturbance in the cerebellar function except the hypertonicity which is probably due to basal ganglion involvement. The biceps, triceps, patellar and achilles tendon reflexes were all normal Babinski's sign and ankle clonus were both absent. Sensation seemed normal, as tested with pin-point, cotton and tuning fork. The position sense and stereognosis were good There was a fine tremor of the hands noticed particularly when they were at rest. Associated arm movements were lost. The objective picture was one of paralysis agitans

June 13, three days after admission, the patient became stuporous Her mouth remained open and her tongue was dry The pulse was rapid and small, registering 130 An examination of the heart and lungs showed them to be normal Fetal heart sounds were heard in the right lower quadrant. June 27, the temperature began to rise and registered 101 at noon

June 29, she was delivered of an apparently normal baby She delivered spontaneously in bed. She made no outcry and the attendants did not even know that she was in labor The placenta and membranes were expelled intact, and the uterus contracted promptly

The temperature was normal until June 27, when it rose to 101 F After labor it returned to normal and so it remained until July 5, when it rose rapidly to 102 The patient died, July 7, eight days after labor Permission for autopsy was refused.

Appearance of patient one day after delivery

The baby, at birth, so far as could be determined, was a perfectly normal, healthy, full term child. When seen, April 23, the baby was found to be in good health.

CONCLUSIONS

1 Women suffering from chronic epidemic encephalitis are not rendered sterile thereby

2 The incidence of abortion in the patients who conceive is about the same as in the nonparkinsonian individual

3 Pregnant women are not especially susceptible to acute encephalitic infection

4 Clinically the disease pursues about the same course in the pregnant as it does in the nonpregnant woman, though the mortality rate is somewhat increased

5 Pregnancy may aggravate latent or quiescent symptoms of encephalitis in patients who have been previous victims of the disease

6 Women becoming infected with acute encephalitis during pregnancy are especially prone to develop parkinsonism as a sequel, the incidence being from 75 to 80 per cent In the nonpregnant woman the incidence does not exceed 25 per cent

7 Chronic encephalitis does not influence pregnancy with its culmination in labor adversely, save in a small percentage of cases

8 Accumulated evidence tends to show that pregnancy has a decidedly unfavorable effect on parkinsonism

9 While it is possible for encephalitis to be imparted to the unborn child, transmission of the disease to the fetus seems to be exceedingly rare

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RUPTURE OF THE BLADDER

A PLEA FOR ITS EARLY DIAGNOSIS AND TREATMENT *

GEORGE de TARNOWSKY M D
CHICAGO

In an endeavor to outline and classify the essential observations and symptoms which ought to make possible an early diagnosis of ruptured bladder, all cases of trauma to this viscus admitted to the Cook County Hospital during the years 1926-1929 both in my service and in that of my colleagues were reviewed and analyzed, to these were added private cases and those admitted to the Ravenswood Hospital, about fifty cases in all

Convinced that rupture of the bladder is as much a surgical emergency as any coming under the general classification of "acute abdomen" and that the present high mortality is to a large extent due to unnecessary delay in diagnosis, I collectively tabulated and analyzed salient symptoms in order to separate the constant from the occasional, the pathognomonic from the contributory clinical finding In the study of these fifty cases, the conviction is forced on one that a large percentage came under the primary care of colleagues unfamiliar with traumatic surgery Constructive criticism alone justifies mentioning one case in which twenty-two days was allowed to elapse before an extraperitoneal rupture was recognized and operated on In this instance too much reliance had been placed on roentgenologic and cystoscopic examinations, both of which gave negative results Another extraperitoneal rupture was referred to my service for drainage of a right lumbar abscess which was found to contain extravasated urine that had passed retroperitoneally from the space of Retzius An intraperitoneal rupture was undiagnosed for several days because a concomitant fracture of the right forearm had engaged the attending physician's entire attention and only the onset of an apparent ileus disclosed the major lesion An elderly woman lived for three days following an automobile accident In spite of repeated catheterizations of bloody urine, no surgical intervention was attempted and the coroner's report disclosed a fracture of both pubic rami and extraperitoneal rupture of the bladder with extravasation and infection

Less than 5 per cent of bladder ruptures are caused by or accompany pelvic fracture (one case in twenty fractured pelves, Ravenswood Hospital, 1926-1929, three in forty-two bodies, Cook County Hospital, 1911-1924), and cystoscopy will be negative if (*a*) in extraperitoneal rupture the tension of the extravesical fluid equals that within the bladder, or (*b*) the rent in the serosa and muscularis is overlapped by a fold of mucosa The probability of multiple injuries being present is frequently overlooked Fracture of the forearm, laceration of the right supra-orbital region, contusion of the right leg and of the right hip and bilateral inguinal hernia were some of the outstanding injuries that masked a coincident trauma to these patients' respective bladders When the patient is intoxicated or unconscious, or no history of the case is obtainable because of linguistic difficulties, failure to make a correct primary diagnosis is readily understandable Of the Cook County series, two cases, one of cerebral concussion and the other with no history of trauma but symptoms of intestinal obstruction present, come under this heading

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* Read before the Chicago Surgical Society April 4 1930

* From the department of surgery University of Illinois College of Medicine.

ANATOMIC CONSIDERATIONS

The bladder is suspended in the anterior portion of the pelvis by the urachus above and is firmly attached to the prostate and rectum at the rectovesical pouch The so-called ligaments of the bladder are merely reflections of the pelvic fascia It is firmly fixed only at its upper and lower portions Separated from the symphysis anteriorly by the prevesical space of Retzius, the bladder is nowhere in intimate contact with the pelvic bones Very rarely are spicules of bone found which have penetrated the bladder wall (none in the forty-two Bacon-Le Count series), they are never found in intraperitoneal ruptures, which almost invariably involve the upper posterior wall

The capacity of the bladder varies within wide limits among different individuals and in the same individual at different times Distention of the rectum by gas and feces increases the frequency of desire to urinate Habit and environment exert an important influence An individual who can always do so will empty his bladder at the first inclination, under stress of social customs he may have to postpone the act in spite of desire, women are peculiarly apt to curb this inclination Automobile trips frequently create situations in which the bladder becomes overdistended, hence the number of ruptured bladders reported in recent years as the result of automobile accidents While the normal bladder capacity has been estimated as lying between 350 and 500 cc, pathologic changes may decrease its distensibility to a marked degree Rejsek[1] reports injecting 120 cc of contrast suspension for roentgenography of the bladder of a 68 year old man This was immediately followed by severe spasm of the bladder, and the roentgenogram revealed a rupture of the bladder wall The patient recovered after drainage of the space of Retzius A man, aged 57, came to Bitschai's[2] clinic for the treatment of hematuria During cystoscopy, which revealed a papillary carcinoma of the bladder, a spontaneous rupture occurred Progressive paralysis, tuberculosis of the bladder and diverticula may also lead to atraumatic rupture Gottlieb[3] created an intraperitoneal rupture of the bladder while performing a lithotripsy His patient was a man, aged 57 After closing the tear, he poured 75 cc of ether into the pelvic cavity The patient recovered Coplan's[4] patient was a man aged 42, who during a drunken bout developed what was at first diagnosed as acute gastritis The true pathologic condition was recognized twenty-four hours later at laparotomy An intraperitoneal tear was found, owing to the presence of severe shock, the bladder was not sutured and under prolonged drainage the patient eventually recovered Malcolm[5] also reported the case of a man, aged 30, who, while drunk, was put in jail, although he complained of severe abdominal pains A working diagnosis of ruptured gastric ulcer was made, after the stomach was found to be normal, the abdominal incision was prolonged toward the pubis A rupture of the bladder had occurred in two places, both on its posterior wall The tears were sutured to the parietal peritoneum, after the bladder had drained for nine days the fistula was allowed to close by granulation tissue The patient recovered in six weeks Jilow[6] found a 4 cm intraperitoneal rupture of the bladder in an alcoholic addict, aged 44, there was no history of trauma obtainable Chronic stricture of the urethra has been known to cause spontaneous rupture of the bladder[7]

In extraperitoneal rupture of the bladder there may be rare instances of actual puncture of this viscus by a spicule of bone if the trauma is very violent, in most cases the rupture occurs as a result of a sudden pull on the lateral true ligaments if the bladder is empty Bacon and Le Count did not find any bone spicules in the bladders in their reported cases[8] Direct trauma of the suprapubic area may be transmitted to a distended bladder and cause a rupture, as occurred in a Cook County case All intraperitoneal ruptures are of the bursting variety, a further subdivision into spontaneous or pathologic and traumatic clarifies the picture By spontaneous should be understood a tear of the bladder without external or internal stimulation Besley,[9] in 1907, reported one spontaneous rupture in twenty-five cases analyzed from the Cook County services Five are reported in the present series, two of them may be classed as doubtful because they occurred in alcoholic patients

In children the bladder is practically an abdominal organ, when it is empty the peritoneum sinks about to the level of the top of the symphysis, but when it is distended it rises from 2 5 to 6 25 cm above In the adult the top of the bladder is held to the top of the symphysis by the urachus, and as it becomes empty the upper surface descends until a curved line is formed from the top of the symphysis downward and backward to the retrovesical pouch When bladder and rectum are both empty, the former lies at the bottom of the pelvis When the rectum is distended by gas, feces or both, the bladder is raised so that its fundus or vertex reaches to or nearly to the upper border of the symphysis When the bladder begins to distend, the rectum being empty the distention begins in the posterior part of the bladder and continues to be greatest in this portion The weakest part of the bladder wall is in its posterosuperior hemisphere, tearing occurs in the direction of the longitudinal muscle fibers, which tend to spread out and allow a diastasis of the bladder mucosa (Jeanbrau[10]) The shape of the bladder, when distended is also considerably modified by the full or empty rectum. When the latter is empty the floor of the bladder descends, expands anteroposteriorly and laterally and rises only moderately. With a distended rectum the pelvic space is limited and the bladder rises into the abdominal cavity. Fehleisen[11] found the relations presented in table 1 between the peritoneal fold and the symphysis under different conditions of distention of the bladder and rectum.

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[1] Rejsek J Rare Case of Rupture of Bladder During Roentgenography of Bladder J d urol **20**: 382 387 (Nov) 1925

[2] Bitschai J Spontaneous Rupture of Bladder Case Ztschr f Urol **21** 461-464 1927

[3] Gottlieb J C Case of Rupture of Bladder Caused by Lithotripsy Ztschr f Urol **22** 469-471 1928

[4] Coplan M M Intraperitoneal Rupture of Bladder with Report of Case, J Florida M A. **13** 182 185 (Feb.) 1927

[5] Malcolm R. B Rupture of Bladder Canad M A J **15** 1151 (Nov) 1925

[6] Jilow N N Spontaneous Rupture of Bladder Case Zentralbl f Chir **55** *780 (March 31) 1928*

[7] Williams L. H Multiple Scrotal Fistulae Following Rupture of Bladder with Stricture of Urethra Operation and Restoration of Function U S Nav M *Bull* **25** *897 898* (Oct) *1927*

[8] Bacon L. H and LeCount E. R Automobile Injuries A Study from Records of Postmortem Examinations Arch Surg **18** 769 802 (March) 1929

[9] Besley F Ruptures of Urinary Bladder Surg Gynec. Obst **4**: 514-520 1907

[10] Jeanbrau, E. Pathologie chirurgicale **5** *376-380* 1928

A distended bladder ascends out of the pelvis and rests directly against the anterior abdominal wall.

TABLE 1.—*Relation of Position of Peritoneal Fold to Degree of Distention of Bladder*

Bladder	Rectum	Peritoneal Fold Above Symphysis
300 cc.	Empty	0.5 cm.
200 cc.	Full	4.0 cm.
630 cc.	Empty	2.0 cm.
420 cc.	Full	8.5 cm.

Besley proved experimentally on cadavers that it only took from 9 to 17 pounds (4 to 7.7 Kg.) pressure to rupture a bladder wall. While admitting that in a cadaver the elasticity of the muscle fibers had been lost, to offset this disadvantage is the fact that the pressure was applied slowly and carefully. One must conclude from these significant experiments that a very slight trauma to the lower anterior abdominal wall, directly transmitted to a distended bladder, can be sufficient to cause a rupture of the latter.

Extraperitoneal rupture takes place into the prevesical space of Retzius; from this region urine and blood may invade the subcutaneous spaces as low as both knees or as high up as the umbilicus. It also can penetrate the subperitoneal tissues of the pelvis and abdomen and reach the perinephric tissues.

ETIOLOGY

I have tabulated the type of trauma responsible in the analyzed series (table 2).

Thus of the analyzed series of ruptures, 40 per cent were caused by automobile accidents, i. e., the injured being drivers or passengers of cars. It is safe to state that in a majority of these patients the lower abdominal wall came in sudden contact with the steering wheel or dashboard. Given an overdistended bladder lying against the anterior abdominal wall plus a sudden "off-guard" bump and one has the bursting injury which is the typical finding in a majority of bladder ruptures. While some of the patients, especially the alcoholic addicts, are notoriously vague as regards a full or empty bladder at the time of an accident, those who did remember reported that they had not voided for several hours prior to the collision. Caulk's[12] case is typical. A 6 year old girl, living on a farm, was leaving the loft in which she had spent the night with her mother when she slipped on the floor and a horse stepped on the lower part of her abdomen. Her bladder was necessarily overdistended; no fracture of the pelvis was found but there was a bursting rent of the base of the bladder just lateral to the right margin of the trigon. In Besley's report, falls and crushing injuries accounted for 60 per cent of his cases.

TABLE 2.—*Type of Trauma Causing Rupture*

Automobile accident	20
Crushing injury	10
Falls	10
Kick on lower abdomen	3
Indirect (no history of trauma)	3
Fall on buttocks	2
Saddle-horn trauma	1
Stepped on by horse	1
	50

Next to automobiles, falls and crushing injuries claim the largest percentage of victims, and it is in this group that most cases of fractured pelves and almost all of the extraperitoneal lacerations of the bladder are to be found. Alcoholism, strictures of the urethra, prostatic hypertrophy and pathologic changes in the bladder wall (carcinoma, tuberculosis, chronic cystitis) are important concomitant factors. Brenner[13] reports that a man, aged 56, who was walking to the toilet to empty a full bladder, slipped and fell on his buttocks. There was no trauma to the pubic region. A 4 cm. tear was found, beginning at the peritoneal reflexion. Hoffman's[14] patient, aged 43, slipped on ice and fell on his buttocks, bursting his bladder.

SYMPTOMS AND DIAGNOSIS

I have tabulated the signs and symptoms taken from the fifty analyzed histories in order to bring out the salient points (table 3).

TABLE 3.—*Symptoms Present in Fifty Cases of Ruptured Bladder*

Total number of cases analyzed	50
Pain and tenderness over pubes	45
Vesical tenesmus	40
Lower abdominal distention	40
Bloody urine	25
No post-traumatic urination	22
Swelling of inguinal region, scrotum or vulva	12
Bloody urine in peritoneal cavity	12
Clear urine on catheterization	5
Shock	5
Vomiting	5
Blood alone voided or catheterized	4
No urine on catheterization	3

From the foregoing it would seem evident that, given a history of trauma, however slight, followed by pain and tenderness in the suprapubic region, vesical tenesmus and lower abdominal reaction, one should suspect possible injury to the bladder. Bloody urine or no post-traumatic urination is a frequent symptom. Blood may be voided once or not at all; the site of the tear may not include any sizable blood vessels. Blood alone may be voided if all the urine finds its way into the peritoneal cavity and the tear is near the trigon. Cystoscopy may be of great value, especially in incomplete ruptures or traumatic herniations of the bladder wall; it may be dangerous if attempts are made to remove blood by irrigation, and the cystoscopic report should not be given undue weight—it is merely corroborative.

The catheter should be used early and repeatedly, preferably at two hour intervals if there is still any doubt regarding the exact diagnosis. Bloody urine, clear urine with or without a trace of albumin or no urine may be the reward of catheterization. Clear urine may throw the surgeon off the right track unless he checks up on the quantity obtained or spontaneously voided. The patient's statement as to the presence or absence of bloody urine is usually unreliable. If the intraperitoneal tear is a large one, urine and blood freely enter the peritoneal cavity and are as readily withdrawn In one case of the Cook County series, 7,775 cc of urine was recovered by catheterization at one time This patient, a man, aged 32, had been kicked in the lower part of the abdomen while intoxicated He remained unconscious for several hours then went home and vomited several times Following catheterization, the history states "he went into a serious condition suggesting right cerebral hemorrhage" Death occurred on the third day after admission, presumably four days after the kicking The true diagnosis of intraperitoneal tear of the bladder was not made until after death

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[11] Fehleisen, A.: Arch. f. klin. Chir. **32**: 563, 1885.

[12] Caulk, J. R.: Rupture of Bladder in Child, J. Urol. **19**: 603-611 (May) 1928.

[13] Brenner, A.: Rupture of Bladder, Wien. klin. Wchnschr. **39**: 328-329 (March 18) 1926.

[14] Hoffman, C. G.: Traumatic Rupture of Urinary Bladder: Report of Two Cases, South. M. J. **18**: 680-684 (Sept.) 1925.

Shock and vomiting are only occasionally present, if they appear at all it is usually several days after the accident, when infection has set in World War wounds of the bladder were almost invariably accompanied by profound shock, but there were many factors present that are not found in civil traumatisms Pulse, temperature, respirations and leukocyte count are utterly unreliable except as a general indication that there is a systemic reaction against something, somewhere

The Vaughan-Rudnick test[15] is accurate but should be unnecessary in the vast majority of cases If more than 100 cc of air is used there might be some danger of completing a hitherto incomplete rupture of the bladder Moreover, it demands a technic and armamentarium not always available The roentgenogram will diagnose fractures of the pubic rami ischial tuberosities or sacrum, but, as shown elsewhere in this paper, approximately only 5 per cent of fractured pelves are associated with rupture of the bladder

The old classic method of injecting a measured quantity of sterile fluid and then removing and measuring it belongs to the period of 100 per cent mortality and should not be used Suprapubic puncture is both unnecessary and unreliable In a case in the Cook County Hospital series suprapubic puncture was negative, although a few hours later 1,000 cc of bloody urine was found in the peritoneal cavity

Of the later symptoms discoloration and edema of the suprapubic area, the inner sides of both thighs, the perineum and the scrotum in the male and the vulva in the female are perhaps the most common Peritonitis is not a frequent early sign of an intraperitoneal rupture, urine may fill the pelvis and lower part of the abdomen with little or no peritoneal reaction, occasionally in all probability as a consequence of antecedent cystitis, a generalized peritonitis may develop within twenty-four hours of the accident Occasionally a patient will make a leading statement which ought to put the surgeon on the right track One man said he felt something give way inside him Peak[16] had a 20 year old patient who declared he knew his bladder was ruptured because he could feel blood or urine oozing toward the left side of his pelvis and there was a sensation of warmth in his side"

DIAGNOSES IN THE FIFTY ANALYZED CASES

In the fifty analyzed cases a correct primary diagnosis was made in thirty-four or 68 per cent a delayed diagnosis in ten, or 20 per cent, and a missed diagnosis in six or 12 per cent

Incorrect diagnoses included ruptured gastric ulcer acute gastritis, abdominal bruise appendicitis pneumonia pyelitis, strangulated hernia, hematoma, cerebral concussion and intestinal obstruction

The importance of early diagnosis and operation is graphically brought out by the analyses presented by the following authors

Negley[17] Operation in first twelve hours, 11 per cent mortality, operation in twelve to twenty-four hours, 22 per cent mortality, operation on second day, 43 per cent mortality

Rouvillois and Ferron[18] Operation in first twelve hours, 11 per cent mortality, operation on second day, 43 7 per cent mortality

Cook County Hospital series Operation within twenty-four hours, 26 per cent mortality, delayed operation, 45 per cent mortality

MORTALITY

It is well nigh impossible to estimate correctly the mortality of bladder ruptures per se Multiple injuries alcoholism or antecedent pathologic changes in the bladder wall all tend to obscure the situation Single cases are usually reported if the patient recovers it is only through analysis of a series of cases that a fair estimate of the prognosis of bladder ruptures can be obtained While modern diagnostic measures and proper technic can now refute Hamilton's dictum that a ruptured bladder inevitably means death of the patient,' there is still much room for improvement

TABLE 4—*Analysis of Fifty Cases of Bladder Rupture Since 1926*

Type	Number of Cases	Mortality
Intraperitoneal	35	48%
Extraperitoneal	15	42%

Up to the year 1907, Besley's twenty-five cases showed a mortality of 78 per cent Of thirteen patients admitted to the same hospital during the years 1927-1929, eight died, a mortality of 61 per cent In the thirty-five cases reported since 1905 and tabulated by Hagenbuch[19] the mortality was 60 per cent Negley reviewed 124 cases with a mortality of 53 per cent The average mortality in the fifty cases analyzed in this report was 45 per cent with only a 6 per cent difference between intraperitoneal and extraperitoneal rupture

A review of the combined reports of the past few years proves conclusively that there is still a mortality of more than 50 per cent in cases of bladder rupture and that the mortality in this type of trauma could be easily lowered to 20 per cent or less if early diagnoses were more frequently made and operative procedures promptly carried out

TREATMENT

Expectant Treatment—In rare instances in which, in spite of pain vesical tenesmus and bloody urine the systemic reaction is mild or absent one may be justified in adopting an expectant attitude being prepared to operate as soon as the clinical picture changes for the worse Particularly is this true in (1) incomplete ruptures (2) small linear tears of 1 cm or less and (3) traumatic diverticulitis of the bladder In all three conditions, a prerequisite to nonsurgical treatment is a satisfactory cystoscopic examination. The catheter-a-demeure should always be used for at least one week, following which the patient must be instructed to avoid diurnal or nocturnal bladder distention for another ten to fourteen days. Two typical cases are included in this series.

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[15] Vaughan R T and Rudnick, D F A New and Early Sign of Ruptured Bladder J A M A 83: 9 (July 5) 1924

[16] Peak, J H Traumatic Rupture of Urocyst with Report of Case Kentucky M J 24 190-192 (April) 1926

[17] Negley J C Rupture of Bladder J Urol 18: 307 314 (Sept) 1927

[18] Rouvillois and Ferron quoted by Negley (footnote 17)

[19] Hagenbuch M Rupture of Uterus with Laceration of Bladder in Connection with Personal Case Ztschr f Geburtsh u Gynak. 89 810 1925

Case 1 (Ravenswood Hospital, Dr E. B Williams).—In a middle-aged woman, the victim of an automobile accident, roentgenography showed fracture of the right radius and styloid process of the right ulna, fracture of both the horizontal and descending rami on both sides, with some slight downward displacement of the pubic fragments anteriorly.

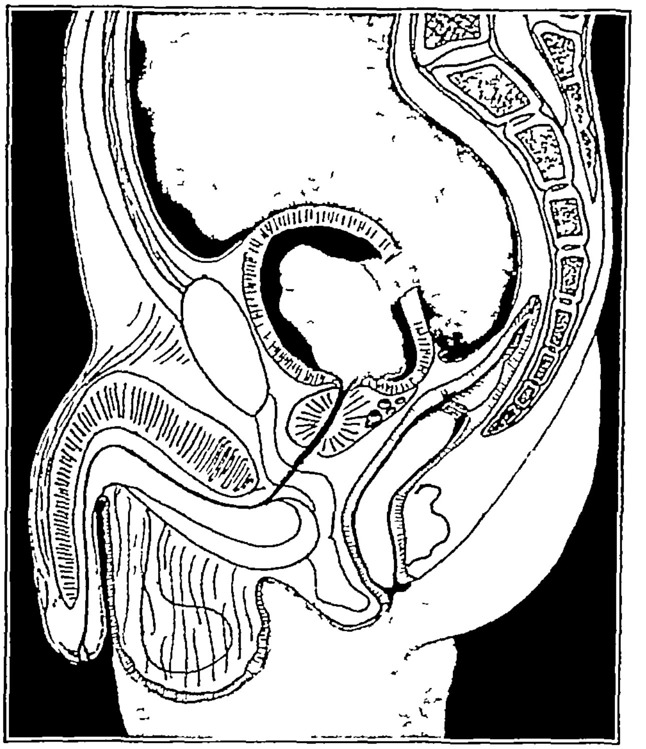

Fig 1.—Intraperitoneal rupture.

The patient voided bloody urine on the day of the accident and complained of pain in the pubic region with vesical tenesmus. On the second day the vulva became edematous. Cystoscopic examination revealed a 1 cm. tear just to the right of the median line and about 2 cm. from the urethra. Expectant treatment was advised and carried out. Bloody urine passed by catheter for more than one week, but after a somewhat stormy and protracted convalescence the patient left the hospital cured.

Case 2 (reported by Caulk[12]).—A girl, aged 6 years, had a horse step on the lower part of her abdomen after she had slipped and fallen down on the floor of a farm stable. Her bladder was full at the time of the accident. The immediate complaints were soreness and tenderness over the lower part of the abdomen, vesical tenesmus and inability to urinate. Three hours later the leukocyte count was 24,000. A catheter was introduced in the bladder and 200 cc. of bloody urine was withdrawn, then 100 cc. of sterile fluid was injected and withdrawn. A roentgenogram did not show fracture of the pelvis. The patient was treated expectantly with a catheter-a-demeure. On the sixth day the bladder was examined cystoscopically and a rent about 2 cm. in diameter showed itself. It was situated on the base of the bladder just lateral to the right margin of the trigon, approximating the internal sphincter. The hole was irregular, ragged and covered with a great deal of fibrin and slough. The rest of the bladder was perfectly normal. At no time, apparently, was there any clinical evidence of urinary extravasation. Using a contrast solution, Caulk took successive roentgenograms which showed progressive obliteration of the diverticulum. The child made a complete recovery.

It is to be noted that in both cases no clinical evidence of urinary extravasation manifested itself. In spite of their happy outcome, the expectant line of treatment will rarely be advisable, certainly in not more than 5 per cent of all cases.

Operative Treatment.—1. Extraperitoneal rupture. (*a*) A median suprapubic incision is made through the skin and fascia, the fibers of the pyramidal muscles are separated by blunt dissection and the fat and loose connective tissue of the prevesical space are pushed to one side. It should be borne in mind that, in making an incision just above the pubis, three layers of fat are encountered: (1) the fat between skin and muscles, (2) the fatty pad between the posterior surface of the muscles and the transversalis fascia, and (3) the prevesical fat of the space of Retzius. The lacerated bladder being empty, care must be taken not to penetrate the peritoneal cavity at this stage. All urine and blood should be sponged out and the space of Retzius freed from clots.

(*b*) The peritoneal reflexion is pushed up and fine artery forceps are placed on the upper margin of the tear. After the bladder has been irrigated with warm physiologic solution of sodium chloride, the interior is examined for possible bone spicules and these are removed if found.

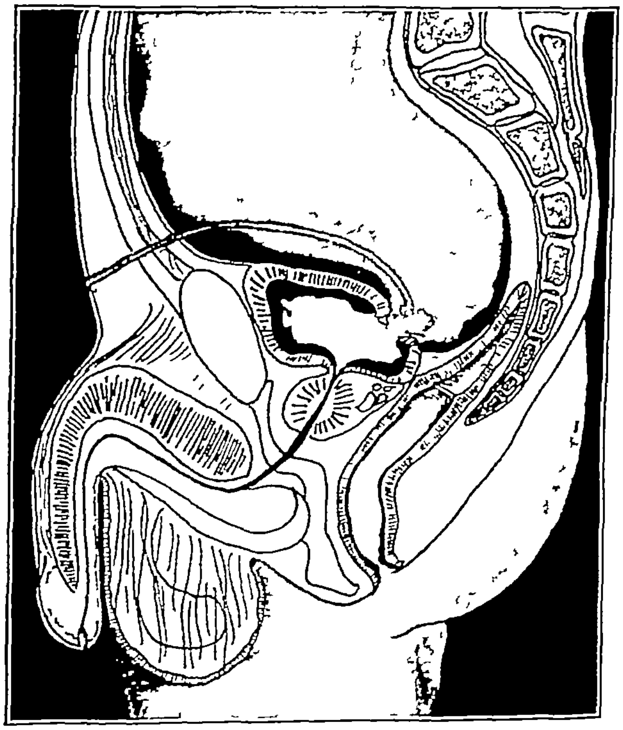

Fig 2.—Operative treatment of intraperitoneal rupture: drain in cul desac after suture of tear.

(*c*) The vesical tear should be sutured by means of nonpenetrating sutures, any suture material penetrating through the bladder mucosa will act as a nucleus for future stone formation. Two layers of sutures are required: (1) a continuous number 0 catgut suture including all coats but not traversing the mucosa and

(2) a Lembert or Cushing right angle suture of fine linen or silk which includes the surrounding fascia By utilizing superficial fascia and some fibers of the pyramidalis muscles, it is usually possible to obliterate the prevesical space almost completely

(*d*) A small cigaret drain is left in the Retzius space and the skin incision closed If the tear is a linear one, its edges are not badly lacerated, and the lines of suture do not tear readily, the catheter-a-demeure may be dispensed with If one is in doubt, 100 cc. of saline or boric acid solution may be injected through the urethra and the space of Retzius watched for leakage Should any fluid appear, the closure may be reinforced with one or more additional silk or linen sutures and the catheter-a-demeure used If omitted, the latter can always be introduced during convalescence should the bladder show signs of overdistention or of extravasation

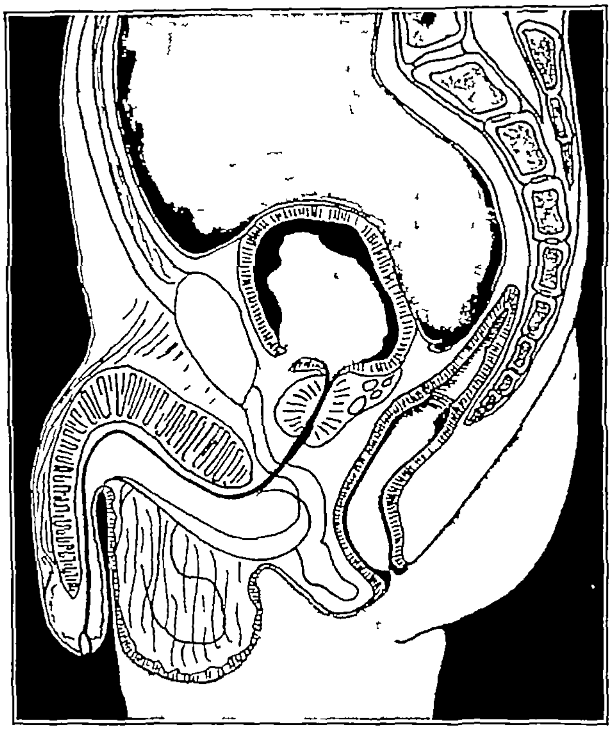

Fig 3 —Extraperitoneal rupture

In the presence of a badly lacerated anterior wall, when the sutures tear out, it is safer not to attempt any closure of the bladder wall A tube drain should be placed in the bladder and anchored to the skin, and the space of Retzius packed with gauze On the following day a catheter is introduced through the urethra Vesical drainage should be maintained for one week, urethral drainage, a few days longer It will take from three to six weeks for the vesical fistula to close

(*e*) Should a fracture of the pelvis be present it is best treated by using the canvas sling suspended to a Balkan frame devised by Douglas P Murphy, late of the American Expeditionary Forces[20]

(*f*) One should watch for signs and symptoms of urinary extravasation, especially along the retroperitoneal spaces Systemic reactions such as chills, sudden rise in temperature and high leukocyte count should initiate a careful examination of all possible fascial plane infiltrations Multiple incisions are often required in these late complications In a patient in the Cook County Hospital series, a boy, aged 14, a correct diagnosis had not been made for eleven days The roentgenogram was positive for fracture of the pelvis, the boy complained of pain and tenderness in the lower part of the abdomen, but, because the urine was free from blood and albumin, the vesical injury was overlooked until he was transferred The ruptured bladder was repaired, but four days later he developed signs of a left perinephric abscess which necessitated a nephrectomy Five weeks later the patient was discharged from the hospital, cured A correct primary diagnosis would have prevented the loss of his left kidney

2 Intraperitoneal rupture (*a*) The suprapubic incision is prolonged upward as far as the umbilicus and the peritoneal cavity is entered All bloody urine is suctioned out, the sigmoid flexure is retracted, with loops of small intestine, and all blood clots are mopped out from the culdesac

(*b*) When the bladder tear has been identified, fine forceps are placed on its upper extremity and gentle traction is made in order to bring the torn edges in alinement The rent is closed, as in the extraperitoneal type Some surgeons test the efficacy of their sutures by injecting boric acid solution into the bladder, this step is not recommended in intraperitoneal tears The rupture has, in a few instances, been repaired through a cystotomy incision this leaves two lines of scar tissue instead of one and lessens bladder distensibility A catheter-a-demeure should be passed through the urethra and kept there for from three to five days

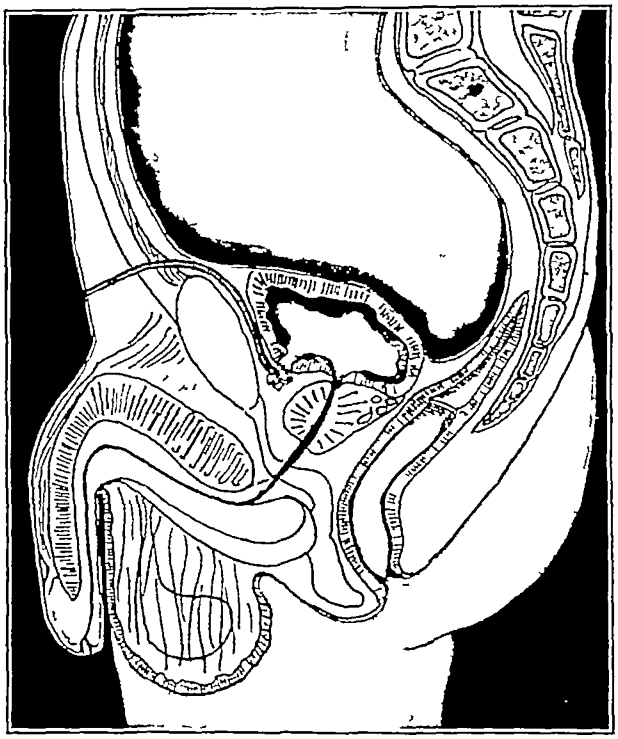

Fig 4 — Operative treatment of extraperitoneal rupture drain in space of Retzius after suture of the tear

(*c*) In desperate cases (severe shock multiple injuries) marsupialization of the laceration may be performed by freeing the parietal peritoneum around the abdominal incision and coapting its edges to the bladder rent Malcolm used this method in the repair of a 2 inch tear in the posterior bladder wall, leaving a drainage tube for nine days His patient was cured in six weeks Occasionally the tear may be as low down as the margin of the trigon and sutures may be difficult or impossible to place accurately unless the surgeon has very sharply curved needles, perfect exposure and light and a dry field In such cases one should place a catheter through the tear into the bladder, suture the upper portion as well as possible around it and place a modified cigaret drain against the lower, unsutured or partially sutured bladder wall This drain should have a rubber tube in its center with gauze freely protruding from its lower end, so that it can be packed against the posterior bladder wall Aspiration of the pelvic cavity can be carried out by means of the central tube The space of Retzius should be obliterated by means of interrupted catgut sutures and the skin incision closed with the drain issuing from its upper angle After operation, aspiration of the culdesac tube should be done three times daily, when it has yielded negative results for three or four days, the entire cigaret drain is removed The catheter-a-demeure can be removed as soon as the peritoneal sinus created by the cigaret drain is closed It should always be used regardless of the method of treating the vesical tear Negley mentions what ought to be a valuable aid in small lacerations When starting the anesthetic, he injects 10 cc of an 0 8 per cent solution of indigocarmine intravenously The dye will appear in the bladder urine and help locate the tear

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[20] De Tarnowsky George Emergency Surgery p 427

TABLE 5—*Operative Technic in the Fifty Analyzed Cases*

Suture of tear	39 cases
Drainage without suture	5 cases
Suprapubic bladder drainage	2 cases
Closure of tear through bladder incision	1 case
Marsupialization	1 case
No operation (expectant)	2 cases

CONCLUSIONS

1 Automobile transportation has multiplied the number of daily collisions Both the driver with the steering wheel in front of him and the occupants of the front seat with the dashboard in front of them are likely to suffer trauma of the lower part of the abdomen during collisions or sudden stops of the automobile

2 A large percentage of reported accidents occurred in persons with overdistended bladders, lying against the anterior abdominal wall, this viscus will burst without any trauma to the bony pelvis

3 While multiple injuries or loss of consciousness may at first cloud the diagnosis, pain in the lower portion of the abdomen, vesical tenesmus, bloody urine or inability to urinate should be sufficient to indicate immediately to the surgeon the probable bladder lesion

4 The average mortality from bladder lesions, while unquestionably increased by coincident injuries to other organs or tissues is still too high because primary diagnoses are not being made frequently enough

5 Rupture of the bladder is as much a surgical emergency as 'acute abdomen" and delay in operating is equally dangerous

6 Closure of the tear by suture, prevesical or culdesac drainage and catheter-a-demeure are the three essential operative steps In individual cases the surgeon may have to modify this technic

30 North Michigan Avenue

CULTIVATION OF BRUCELLA FROM THE STOOLS AND BILE

FURTHER OBSERVATIONS *

HAROLD L AMOSS, M D
AND
MARY A POSTON
BALTIMORE

Further experience has resulted in the isolation of *Brucella* from seventy-eight specimens of stools from six patients since July, 1929 In one of these patients, *Brucella* was obtained in cultures from B bile obtained before operation by duodenal drainage and from the contents of the gallbladder removed by Dr J M T Finney[1] Bull and Gram[2] isolated *Brucella* from the gallbladder contents at operation, but we have been unable to find any references to the isolation of this organism from bile obtained in duodenal drainage

The essential procedure of the method[3] is to clump the organisms present with immune serum added to the stool suspension and to concentrate by differential centrifugation The final precipitate is plated on stock eosin-methylene blue plates made with meat extract agar adjusted to p_H 7 4 Four plates are seeded in each instance, incubated at 37 C, two in 10 per cent carbon dioxide, and the others outside Small clear colonies are fished into broth and identified in the usual manner

Two workers, in personal communications, have reported their failure to isolate *Brucella* from the stools by this method Consequently, parallel cultures were made with plates prepared with meat extract agar p_H 7 4 and others in which Huddleston's liver agar p_H 6 6 formed the basis In ten stools known to be positive the two series of plates gave identical results The colonies on the liver agar-eosin-methylene blue plates were no larger, nor did they appear earlier, than on the plates prepared with beef infusion agar at p_H 7 4

Teague Medium

Meat extract agar p_H 7 4	100 cc.
Sucrose (20 per cent solution)	5 cc
Lactose (20 per cent solution)	5 cc
Yellow eosin (4 per cent aqueous solution) W S (E Leitz, New York)	1 cc
Methylene blue (1 per cent aqueous solution) (Bell and Coleman for bacilli)	1 cc

The eosin-methylene blue plates are prepared from the materials listed in the accompanying table The agar is melted and cooled to 45 C, the sucrose, lactose, eosin and methylene blue are added The eosin should be well distributed in the agar before the methylene blue solution is added

COMMENT

Since *Brucella* in general is reported to grow more easily on liver agar, it is logical to use this medium in the isolation of these organisms from the stools In these experiments, apparently the use of the liver medium as a basis for the eosin-methylene blue plates did not improve the method Yet it is possible that some strains may grow better on the liver medium and it is suggested that, in planting stool specimens suspected of containing *Brucella,* the liver medium be used in parallel with the meat extract agar

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* From the Biological Division Medical Clinic Johns Hopkins University and Hospital

[1] Full details concerning this patient H P will be reported by Dr Hugh R Leavell

[2] Bull P and Gram H M Cholecystitis with Pure Culture of M Melitensis Norsk Lægevidensk 9: 1026 1911

[3] Amoss H L and Poston Mary A Undulant (Malta) Fever J A M A 93 170 (July 20) 1929

So far as we know, this is the first time that *Brucella* has been isolated from bile *intra vitam*

Since the publication of the first article, our attention has been called to the fact that Eyre,[4] in 1908, obtained on plates seeded with the light colored feces obtained at autopsy from the colon of a fatal case of malta fever "a mixed growth of a large variety of bacteria, including *Micrococcus melitensis*" We wish to give him credit for the observation in the following quotation from his paper "By emulsifying some of the growth in saline solution, precipitating the micrococci by the addition of a powerful agglutinating serum, and again plating the sedimented micrococci, I was able to obtain it in pure culture "

Eyre was able also to grow *Brucella* from the gallbladder of an infected guinea-pig

There is under observation in our wards at present a patient who experienced a mild attack of *Brucella* infection and is now convalescent The organism was obtained from blood culture, but twelve specimens of stools have been negative for *Brucella* It is probable that the organisms may not be present in the stools in every case

SUMMARY

Brucella has been isolated seventy-eight times from the stools of six patients

The use of liver agar as the basis for the eosin-methylene blue plates offers no improvement over meat extract agar

Brucella has been obtained in cultures from the bile procured by duodenal drainage and from the contents of the gallbladder at operation in a case of chronic *Brucella* infection

The causative organisms may not always be present in the stools of acute cases of *Brucella* infection

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[4] Eyre J W H The Milroy Lectures on Melitensis Septicemia (Malta or Mediterranean Fever) number 2 Lancet 1: 1747 1908

Posterior Pituitary Extracts and Dermal Pigments— Although the standardized rat threatens to usurp the place once occupied by the frog as the principal contributor to physiological knowledge, the frog and its larvae still have ample contributions to make Not only has embryology taught us that the rudimentary hypophysis is the first of the future endocrine organs to be differentiated, but in the tadpole its exposed position lays it open to surgical removal When so removed, as first shown (1916) independently and brilliantly both by Allen and by Smith, the growth of the tadpole is checked, metamorphosis does not occur, and the pigmentary system is so affected that the embryo acquires a silvery or albinous appearance owing to the contraction of the cutaneous melanophores. Reimplantation of the hypophysis or the parenteral injection of fresh pituitary emulsion serves to counteract all these effects but of special interest is the fact, of late strongly reemphasized by Allen that transplants of the pars intermedia from adult frogs into these albinoid tadpoles, while without effect on growth or metamorphosis serve within a few hours permanently to expand the melanophores with darkening of the skin. Here, then is evidence of still another peculiar property of posterior lobe extracts which must be taken into consideration—their influence on the metabolism of dermal pigments.—Cushing Harvey Lister Memorial Lecture Neurohypophysial Mechanisms from a Clinical Stondpoint, *Lancet* July 19, 1930

Clinical Notes, Suggestions and New Instruments

DIABETES INSIPIDUS AND OSTEITIS FIBROSA POLYCYSTICA

ABRAHAM SOPHIAN M D KANSAS CITY MO

In the case of diabetes insipidus here recorded, the following rare and interesting features deserve emphasis (1) the exceedingly rare complication of an extensive osteitis fibrosa polycystica, (2) a most unusual degree of uniform pulmonary fibrosa of interesting origin

REPORT OF CASE

A man aged 39 American, had apparently been well until the age of 25, when an excessive thirst developed, at times the patient drank as much as 15 gallons (60 liters) of water a day with corresponding polyuria This condition continued uncontrolled until he reported to me seven years later With the establishment of diabetes insipidus, pituitary extract (posterior lobe) therapy was stated with complete control of the symptoms

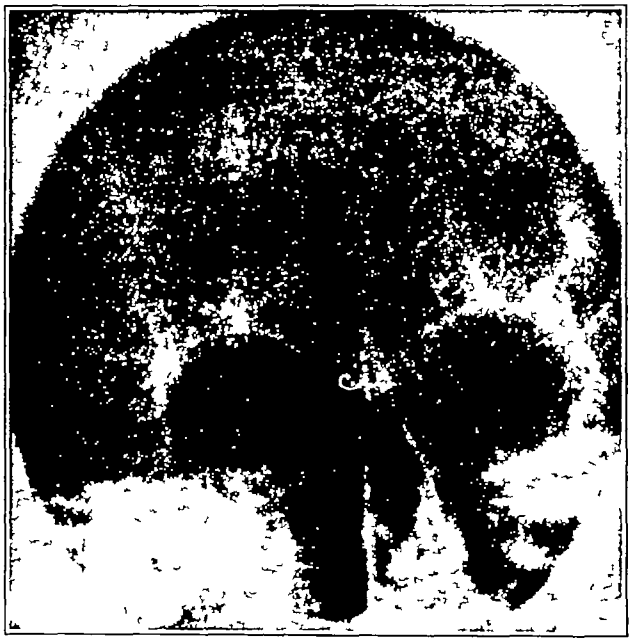

Fig 1 —Large destructive bone area in right frontal region irregular in outline without evidence of new bone formation

Impotence developed shortly after the onset of the polydipsia and has continued unimproved The patient showed steady loss of vigor strength and weight to a total of 60 pounds (27 Kg)

An extensive generalized eczema developed early and has been a persistent feature of the disease

The patient also complained early of persistent joint symptoms referred to the back, shifting to the left hip and then to the left knee, the latter joint becoming red, acutely tender and swollen. This picture of acute joint pain, varying degree of swelling and reduction in function with periods of remission in pain, but persistent swelling and disability, was characteristic of the joint disturbance throughout. It is also of interest that the widely scattered bone lesions later described were not painful, even when accompanied by considerable bone defect, as in the case of the large defect in the right frontal bone

A history of striking extensive focal infection was present. At 10 the patient had a severe crop of boils At the age of 25 he had acute appendicitis with operation At 26 he had considerable trouble with his teeth, which necessitated complete extraction Later there followed a foul nasal discharge for ten years, caused by an extensive polypoid purulent disease of the antrum, this was cured by radical operation

Analysis of the important observations led to a diagnosis of osteitis fibrosa polycystica

A roentgen study was made of many bones showing a generalized type of bone disease with uniform characteristic lesions The long bones, the lower end of each femur, and the upper end of each humerus, the upper end of each tibia, the greater trochanters, the lumbar vertebra, the bones of the pelvis and the cranium all showed cystic areas up to 3 by 5 cm in size, surrounded by areas of bone absorption with no evidence of repair and confined to the medullary portion of the bone

The roentgen studies were made and diagnosis was established by Dr Ira Lockwood of the Research Hospital

Heard, Schumacher and Gordon[1] have stressed the relationship of diabetes insipidus and osteitis fibrosa polycystica and the apparent improvement in both conditions under treatment with pituitary extract.

The case reported here has no traumatic element it is apparently related to the diabetes insipidus The evidences of endocrine disturbance are numerous The bone disease has been steadily progressive and has shown no response over a period of three years that it has been under treatment with pituitary extract

Interesting observations have appeared in the literature on the relationship of parathyroid disease (hyperparathyroidism) to generalized bone disease and notably to osteitis fibrosa polycystica This subject was recently reviewed by Barr and Bulger[2] Most writers agree that hyperparathyroidism produces a hypercalcemia the calcium being extracted from the bones, thereby producing bone disease In turn there is excessive excretion of calcium, and metastatic calcium deposits have been found in the lungs, kidneys, stomach, heart muscle and thyroid The lung deposit is of interest in explaining a most rare degree of pulmonary calcification and fibrosis in this case

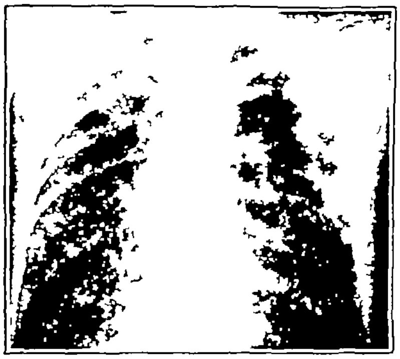

Fig 2 —Extensive fibrosis with calcification The previous print made in 1927 showed a normal chest

Improvement in the bone decalcification has been reported by some observers after the removal of parathyroid tumors The question of a parathyroid operation in the absence of a tumor is however, worthy of serious consideration

The bone cysts and tumors in this disease have been found most frequently in the long bone, but the jaw, pelvis and head have also been involved. Microscopically the tumor lesions have shown hemorrhage, fibrosis and many giant cells, simulating giant cell sarcoma There is also a localized or more general bone decalcification suggestive of osteomalacia. The case here reported showed no increase of blood calcium and the urinary calcium was not determined

THERAPEUTIC OBSERVATIONS

The only specific remedy is pituitary extract, which controls the polydipsia but has no effect on the bone lesions, the dose is inconstant and the drug is as effective by nasal spray as by the hypodermic route, with less constitutional reaction and gastro-intestinal upset.

702 Argyle Building

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[1] Heard J D Schumacher F L. and Gordon W B The Association of Diabetes Insipidus with Osteitis Fibrosa Polycystica, Am J M Sc. **171** 38 (Jan.) 1926

[2] Barr D P and Bulger H A. The Clinical Syndrome of Hyperparathyroidism Am. J M Sc. **179** 449 (April) 1930

Council on Physical Therapy

THE COUNCIL ON PHYSICAL THERAPY OF THE AMERICAN MEDICAL ASSOCIATION HAS ADOPTED THE FOLLOWING REPORT
H J HOLMQUEST Secretary

SUNLIT ULTRAVIOLET GLASS ACCEPTABLE

The window glass known as "Sunlit," submitted to the Council on Physical Therapy for consideration by Semon Bache & Company, New York, is stated to be a glass that transmits the biologic ultraviolet rays of the sun.

According to a test conducted by the Bureau of Standards, this glass does transmit an appreciable percentage of the solar rays which have been shown to have antirachitic properties

The Bureau of Standards report presents data on the transmission of two samples of Sunlit glass for radiant energy of various wavelengths both before and after exposure for ten hours to the total radiation from a 110 volt quartz mercury arc lamp at a distance of about 15 centimeters

Sample Z 26—Thickness 1 88 mm

Wavelength in Millimicrons	Per Cent Transmission	
	New	After Exposure to Mercury Arc
280	41 0	11 5
302	75 4	49 1
313	81 2	60 7
365	91 1	81 7

Sample Z 32—Thickness 2 08 mm

Wavelength in Millimicrons	Per Cent Transmission	
	New	After Exposure to Mercury Arc
280	36 8	9 2
302	71 7	46 2
313	78 5	59 2
365	89 8	79 6

The Council on Physical Therapy declares Sunlit Ultraviolet Health Glass acceptable for inclusion in its list of accepted apparatus for physical therapy

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The Chemical Laboratory

THE FOLLOWING IS A REPORT OF THE AMERICAN MEDICAL ASSOCIATION CHEMICAL LABORATORY PAUL NICHOLAS LEECH Director

SYNTHETIC THYROXINE

Examination of Synthetic Thyroxine, Roche

The story of the discovery and isolation of thyroxine is legend to the medical profession It will be recalled that, following a series of diligent researches, Kendall isolated the preparation from the thyroid gland, he had considered it to be *4,5,6 tri*hydro, *4,5 6 tri* iodo-*alpha*-oxy-*beta* indole propionic acid. Such was the status of the preparation when the U S Pharmacopeia was revised and thyroxine was included *It is* interesting to note the definition in the U S Pharmacopeia X

Thyroxin [$(C_8H_6ONI_3)\,C\,H_4COOH$] is an active principle obtained from the thyroid gland and contains not less than 63 per cent of iodine."[1]

About three years ago, Harington and his co-workers at Cambridge, England, retraced the steps so well laid down by Kendall They arrived at the conclusion that the Kendall formula was not correct and that thyroxine was the tetra iodo derivative of the oxyphenylether of tyrosine. Later this conclusion of theirs was confirmed by the preparation of thyroxine synthetically

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[1] According to the U S Pharmacopeia X thyroxin is spelled without the final e. In view of later developments however it is apparent that thyroxine should be spelled with the final e (as in the case of other basic amino substances) in order to be in keeping with scientific nomenclature.

Since then the sequence has been natural. Synthetic thyroxine has been prepared by pharmaceutic laboratories abroad one brand has been submitted to the Council on Pharmacy and Chemistry A particularly interesting fact is that synthetic thyroxine cannot be considered an official drug because the U S Pharmacopeia definition requires that thyroxine must be the active principle *obtained from the thyroid gland* In view of this, therefore, it was necessary for the American Medical Association Chemical Laboratory, at the request of the Council on Pharmacy and Chemistry, to examine synthetic thyroxine and to publish standards to take care of the nonofficial product even though in the end the identity of synthetic thyroxine and thyroxin U S P might be the same. It is quite likely that in future editions of the U S Pharmacopeia the revision committee will benefit from the experience with thyroxine and not make definitions in the Pharmacopeia quite so exclusive

EXAMINATION OF SYNTHETIC THYROXINE, ROCHE

One original bottle (1 Gm) of Synthetic Thyroxine, Roche, and three bottles [(15 cc) of a 2 per cent solution] (the Hoffman-La Roche Chemical Works Inc., New York City) were submitted to the A M A. Chemical Laboratory for examination at the request of the Council on Pharmacy and Chemistry

The product is stated to be β-[3,5 diiodo 4-(3′ 5′ diiodo-4′-oxyphenyl),-phenyl] α-aminopropionic acid is the diiodo *p*-oxyphenylether of diiodo tyrosine No chemical description physical properties, tests for identity and purity, or methods of assay, other than its molecular weight is 777, were presented by the distributor

The specimen of Synthetic Thyroxine Roche presented occurred as a fine, yellowish white, granular odorless powder The product was found to melt with decomposition (iodine vapors were evolved) between 225 and 228 C The Laboratory found it to comply with the physical properties, tests for identity and purity as given for thyroxin described in the United States Pharmacopeia X The Laboratory, however, substituted the Carius method for the determination of iodine instead of the assay described by the Pharmacopeia

The results of the quantitative determinations were as follows

	Theory	Found by the A M A Chemical Laboratory
Ash		Not weighable
Loss over sulphuric acid		0 65 per cent
Iodine	65 36 per cent	66 35 per cent
Nitrogen	1 80 per cent	Not determined

The Laboratory elaborated standards for inclusion of Synthetic Thyroxine Roche in New and Nonofficial Remedies which appear as part of the description under the acceptance of the product (See Council on Pharmacy and Chemistry report in this issue, page 485)

Council on Pharmacy and Chemistry

NEW AND NONOFFICIAL REMEDIES

The following additional articles have been accepted as conforming to the rules of the Council on Pharmacy and Chemistry of the American Medical Association for admission to New and Nonofficial Remedies A copy of the rules on which the Council bases its action will be sent on application

W A. Puckner Secretary

DIPHTHERIA TOXOID (See New and Nonofficial Remedies 1930 p 364)

Cutter Laboratory Berkeley Calif

Diphtheria Toxoid-Cutter Also marketed in packages of one 45 cc vial

SYNTHETIC THYROXINE — β [3′ 5′-diiodo-4′-(3 5 diiodo-4-hydroxyphenoxy) phenyl]-α aminopropionic acid — $HOC_6H_2I_2OC_6H_2I_2CH_2CH(NH_2)COOH$ A tetraiodo-derivative of *p* hydroxyphenyl ether of tyrosine it contains not less than 65 per cent of iodine

Actions and Uses—See general article Thyroxin, New and Nonofficial Remedies 1930 p 403

Dosage—See general article, Thyroxin New and Nonofficial Remedies 1930 p 404

Manufactured by Hoffmann LaRoche Inc Nutley N J No U S patent or trademark.

Ampuls Synthetic Thyroxine Roche 1 1 cc Each cubic centimeter contains 1 mg of synthetic thyroxine-Roche

Solution Synthetic Thyroxine Roche Each cubic centimeter contains 2 mg of synthetic thyroxine-Roche

Tablets Synthetic Thyroxine Roche 1 mg

Synthetic thyroxine is a white or slightly yellow needle-like odorless crystalline powder

It is insoluble in water and practically insoluble in alcohol or the other more common organic solvents but in the presence of mineral acids it dissolves in alcohol is soluble in solutions of the alkali hydroxides and on saturation with sodium chloride the sodium salt of thyroxine separates Synthetic thyroxine melts with decomposition between 225 and 228 C

Transfer about 0 1 Gm. of synthetic thyroxine to a small hard glass test tube containing a piece of sodium about the size of a pea previously melted after the first violent action has ceased the tube and contents are heated until decomposed vapors of iodine are evolved the tube and contents are allowed to cool add 10 cc. of water the mixture is boiled for a few minutes filter through paper and divide into two portions To one portion add a few drops of sodium hydroxide solution followed by the addition of a few drops of freshly prepared ferrous sulphate solution and finally a few drops of ferric chloride solution and after agitation carefully add diluted hydrochloric acid until the iron hydroxides just dissolve a very finely divided blue precipitate results to the other portion add 1 cc of concentrated nitric acid boil cool and add 1 cc. of silver nitrate solution a curdy yellow precipitate results insoluble in a large excess of stronger ammonia water Add about 0 01 Gm. of synthetic thyroxine to 1 cc. of a one per cent solution of triketohydrindene-hydrate (*Ninhydrin*) solution and boil for one minute a blue color results

Place about 0 03 Gm of synthetic thyroxine in a 50 cc glass stoppered cylinder add 30 cc of water shake the contents for five minutes filter through paper separate portions of 2 cc each of the filtrate yield no opalescence with 0 5 cc of diluted nitric acid and 0 5 cc of silver nitrate solution (*soluble halides*) no turbidity with 0 5 cc. of diluted nitric acid and 0 5 cc of barium nitrate solution (*sulphates*) no coloration or precipitation on saturation with hydrogen sulphide (*salts of heavy metals*)

Incinerate about 0 05 Gm of synthetic thyroxine accurately weighed the residue is negligible Dry about 0 05 Gm accurately weighed for 24 hours over sulphuric acid in a partial vacuum the loss in weight should not exceed 1 per cent Transfer about 0 1 Gm previously dried for 24 hours over sulphuric acid accurately weighed to a bomb tube determine the iodine content by the Carius method the amount of iodine found should not be less than 65 per cent nor more than 66 5 per cent

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COMMITTEE ON FOODS

The following products have been accepted as conforming to the rules of the Committee on Foods of the Council on Pharmacy and Chemistry of the American Medical Association These products are approved for advertising in the publications of the American Medical Association and for general promulgation to the public They will be included in the book of Accepted Foods to be published by the American Medical Association

Raymond Hertwig Secretary

HEINZ RICE FLAKES PREPARED WITH PURE RICE CELLULOSE

Manufacturer—H J Heinz Company Pittsburgh

Description—A flaked rice containing added rice cellulose, yeast salt and milk sugar

Manufacture—Milled rice rice cellulose (7 per cent of weight of rice) yeast (7 per cent) table salt (2 75 per cent) and milk sugar (0 5 per cent) are cooked in a rotary pressure cooker, dried with air flaked toasted cooled and packed

The rice cellulose used is derived from rice hulls The ground hulls are digested with strong caustic soda solution under pressure (which removes silica lignocellulose pentosans and other organic constituents) digested with weak sulphuric acid, washed with water dried and ground

The rice cellulose increases the indigestible residue, the yeast and salt add flavor and the milk sugar improves the color of the toasted flakes

Composition—

	Per Cent
Moisture	1 5
Ash	3 1
Fat	0 3
Protein	7 8
Total carbohydrates (including crude fiber)	80 6
Crude fiber	4 4
Reducing sugars	0 1
Sucrose	0 0
Dextrin	18 7
Soluble starch	37 4
Gelantinized starch	23 4

Claims of Manufacturer—A breakfast cereal with a unique form of water absorptive indigestible cellulose that is less irritant than wheat bran which makes it distinctly beneficial in an anticonstipative diet It is an energy food prominently combined with a new type of laxative feature

RY-KRISP

Manufacturer—Ralston Purina Company, St Louis

Description—A whole rye grain wafer flavored with salt

Manufacture—Flaked whole rye water and salt are beaten with air to a foamy structure The mass is rolled into wafers and baked

Composition—

		Per Cent
Moisture		6 0
Minerals (including added salt)		3 7
Fat		2 0
Protein		13 1
Carbohydrate		73 9
(*a*) Crude fiber	2 2	
(*b*) Pentosans	9 8	
(*c*) Starch	42 4	
(*d*) Dextrins etc	19 5	

Claims of Manufacturer—Ry-Krisp can be used in cases of wheat allergy The wafers encourage thorough chewing Its minerals are relatively higher than those of refined cereals Its bran and cellulose offer means to increase the bulk factor in an anticonstipative diet

MERRELL-SOULE POWDERED SKIM MILK

Manufacturer—The Borden Company, New York

Description—A standard, uniform, practically fat free, powdered skim mill

Preparation—Fresh whole milk from inspected cattle after chemical and biologic examination is mechanically separated The skim milk is pasteurized condensed by distillation of 40 per cent of its water in vacuum pans again pasteurized at 155 F and finally dried by the spray process The canned powder is again processed.

Composition—

	Per Cent
Fat	1 0
Protein	36 5
Lactose	51 8
Mineral matter	7 9
Moisture	2 5

Claims of Manufacturer—This milk powder offers physicians a near approach to a fat-free milk Combined with Klim Powdered Whole Milk" dilutions of increased milk-fat percentage may be obtained if desired

CURTICE BROTHERS CERTIFIED NURSERY FOODS

Manufacturer—Curtice Brothers Company, Rochester N Y

Description—Sieved spinach, carrots and tomato and vegetable puree, prepared by special scientific process and equipment of Curtice Brothers for greater conservation of the vitamins of the fresh product than what is attainable by home sieving and cooking The water content approximates that of the natural raw vegetables

Preparation—The processing equipment largely eliminates the destructive action of air on the vitamins and was developed specially for Curtice Brothers and patent has been applied for The process thereby assures greater protection against vitamin loss in whole or part than do the ordinary commercial processes or home methods

Claims of Manufacturer—These certified nursery foods are especially prepared for babies and young children The manufecturer guarantees a declared minimum number of units of vitamins A B and C for the respective products This information is carried by the can labels The vegetables provide food energy mineral salts to build bones, alkaline salts to counteract acidosis, roughage, and iron for the blood

ALP ROSE CANNED FOODS

Distributor—John Sexton and Company, Chicago

Description—Canned fruits and vegetables, packed in water without added sugar or salt and intended for use in restricted diets The label bears average composition for available carbohydrates, protein and fat

Preparation—Vegetables The vegetables are gathered when in most succulent condition, washed graded as to size and preheated in warm water The water and vegetables are canned sealed and then processed at 245 F for thirty minutes (number 2 cans)

Fruits Mature selected fruit is used It is graded as to size, cored, pitted, or stemmed if necessary, thoroughly washed, canned, and water added to overflowing The cans are exhausted under vacuum, sealed and processed, all at definite temperature and for definite times

Claims of Manufacturer—The selection of the raw materials as to soundness, maturity and section of growth, the preparation for packing, the addition of no salt or sugar, the controlled processing, all lend to standardization of contents and composition of the individual cans for each respective product Laboratory check on this composition and its declaration on the label give a certain assurance and aid valuable to persons on restricted diet

VAN CAMP'S PURÉED FRUITS AND VEGETABLES

Manufacturer—Van Camp Packing Company, Indianapolis

Description—Van Camps Pureed Fruits and Vegetables include purees of peas, spinach, tomatoes, prunes, apricots, carrots with pureed tomatoes and beef broth, and mixed vegetables with beef broth

Preparation—Van Camps Pureed Foods are prepared from selected fruits and vegetables to insure the presence of the natural vitamin and mineral salt values When raw materials such as tomatoes, are subject to oxidation after harvesting only freshly picked stock—fresher than usually available—is used The pureed form is obtained by a precision method of grinding instead of by sieving, which gives a highly uniform comminution of the cellular structures Cooking and other treatment throughout the processes of preparation are carefully devised to prevent the destruction of natural vitamin through oxidation and the loss of mineral salts The processing insures nutritional values equal or superior to those of similar home prepared vegetables and fruits

Claims of Manufacturer—These foods are designed to influence the greater use of certain vegetables of especially good nutritional values, which are considered to be generally slighted in the American dietary, also to provide them in smooth diet form The fruits and vegetables selected for Van Camps pureed foods are chosen for their well established vitamin values They provide an alkaline ash and some indigestible residue The pureed form is introduced because it supplies the cellulose bulk which tends to stimulate normal mechanical function of the intestine without the irritation caused by the coarseness of naturally masticated vegetable fiber which cannot be further disintegrated by any digestive enzyme Preservation of natural flavors and colors is an especial merit of these foods They are especially suitable for smooth diets for gastro-intestinal patients, and for infant feeding

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Disease and the Emotional Life—There are moments, of course in cases of serious illness when you will think solely of the disease and its treatment but when the corner is turned and the immediate crisis is passed, you must give your attention to the patient Disease in man is never exactly the same as disease in an experimental animal for in man the disease at once affects and is affected by what we call the emotional life Thus the physician who attempts to take care of a patient while he neglects this factor is as unscientific as the investigator who neglects to control all the conditions that may effect his experiment. The good physician knows his patients through and through, and his knowledge is bought dearly Time, sympathy and understanding must be lavishly dispensed but the reward is to be found in that personal bond which forms the greatest satisfaction of the practice of medicine—Peabody F W Doctor and Patient New York, Macmillan Company, 1930

MEDICAL EDUCATION IN THE UNITED STATES

ANNUAL PRESENTATION OF EDUCATIONAL DATA FOR 1930 BY THE COUNCIL ON MEDICAL EDUCATION AND HOSPITALS

Part I Premedical Education First Year Students 1929-1930

FOREWORD

After the beginning of its work in 1904 the Council on Medical Education soon found that the United States as a nation had not established supervision over general or professional education nor had it anything to do with the chartering or supervising of educational institutions, these matters having been left to the governments of the several states But this function was assumed in only a few states

In most states, therefore, any individual or group could readily secure a charter giving them authority to open an educational institution and to issue diplomas and conduct their affairs as they saw fit, since no boards or commissions had been created for their supervision In consequence, the most notorious of diploma mills have always been legally chartered"

In a study of conditions regarding high schools which was made in 1906-1907, the Council found that their development had been retarded in certain parts of the country and efforts were made to stimulate their growth An article which had previously been prepared by the Committee of Ten of the National Education Association, headed by President Eliot of Harvard University, was found to contain the outlines of a standard high school course with curriculums for the classical, Latin-scientific, modern language and English high schools, each curriculum requiring a total of twenty study-periods a week This article was published[1] and reprints were distributed to physicians and medical educators, so that information showing what constituted a standard high school was disseminated particularly in the Southern and Western sections of the country

Again no nation-wide list of high schools had been prepared showing which of the several thousand high schools were worthy of bearing that title The Council desired to furnish the deans of medical schools with such a list since a four year high school education was then the minimum requirement for admission to class A medical schools At the request of the Council a list of high schools accredited by state universities or otherwise vouched for was compiled by the United States Bureau of Education

COLLEGE WORK REQUIRED

At the annual session of the American Medical Association in 1912, the Reference Committee on Medical Education added a recommendation to its report to the House of Delegates that beginning Jan 1 1914 a year of college work be required as an essential for the class A rating The requirement was later increased to two years of college work, effective Jan 1 1918

Here again no nation-wide list of colleges deemed worthy of bearing that title could be found In the preparation of such a list the Council gathered such references as it could find whereby an authoritative list of approved colleges could be published for the guidance of prospective medical students and the deans of the medical schools The Association of American Universities had just begun publishing a list of approved colleges made up of the institutions designated by the Carnegie Foundation as worthy of having their professors receive pensions The Southern Association of Colleges and Secondary Schools also was requiring a definite standard for colleges accepted into membership, and the North Central Association of Colleges and Secondary Schools had just established a commission by which certain colleges were listed as approved

At that time the Association of American Universities was the only nation-wide authority having a list of approved colleges but its list was too limited (119) to warrant the Council in restricting its recommendation to the colleges approved by that organization The lists of colleges approved by the district associations of colleges and secondary schools, however provided a larger and more representative list of colleges from which students could be considered for admission to medical schools

Basing its action on such authorities therefore in 1915, the Council issued its first "Provisional List of Approved Colleges of Arts and Sciences" for such value as it might be Since 1915 however this list has undergone a gradual development so that the list revised to June 1, 1930 includes an increased number of colleges which it is believed have been approved by increasingly efficient methods of procedure Lists of approved colleges have been submitted by all of the five district associations of colleges and secondary schools The tabulation also shows which colleges are approved by the Association of American Universities A list of these agencies follows

Lists of Approved Colleges

Associations	Designation	Number of Colleges	
Association of American Universities	A		246
North Central Association of Colleges and Secondary Schools	C	243	
Southern Association of Colleges and Secondary Schools	S	132	
Association of Colleges and Secondary Schools of the Middle States and Maryland	M	100	
Northwest Association of Secondary and Higher Schools	W	30	
New England Association of Colleges and Secondary Schools	N	28	
Total for five districts			533
Total omitting 230 duplicates			549

Following the close of the World War the American Council on Education at Washington was created and has developed as the national center of the five separate district associations of colleges and secondary schools Since 1920, also the American Council on Education has published annually in the *Educational Record* a single and complete list of all of the colleges approved by the several district associations

(Continued on page 497)

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[1] Published by the American Book Company Chicago Reproduced by permission in The Journal July 6 1907 pp [illegible]

TABLE A.—*Sources of Premedical Education First Year Students 1929-1930*

NAME OF COLLEGE	Accredited Agencies Approving	1 Year		2 Years		3 Years		4 Years		Totals		Grand Total
		No Degree	Degree	No Degree	Degree	No Degree	Degree	No Degree	Degree	No Degree	Degree	
ALABAMA		21	5	25	6	16	6		27	62	44	108
Alabama College Montevallo	S								1		1	1
Alabama Polytechnic Institute Auburn	S	4		3					3	7	3	10
Birmingham Southern College Birmingham	A-S	4				1	1		3	5	4	9
Howard College Birmingham	A-S	1				1	2		3	2	5	7
Spring Hill College Spring Hill	S			3						3		3
Talladega College † Talladega									5		5	5
Union College Eufaula						1				1		1
University of Alabama University	A-S	12	5	10	6	13	3		11	44	25	69
Woman's College of Alabama Montgomery	S								1		1	1
ARIZONA		2	1	2	1	7	1		3	11	6	17
Arizona State Teachers College Flagstaff		1				3			2	4	2	6
Phoenix Junior College * Phoenix	C			1						1		1
University of Arizona Tucson	A-C	1	1	1	1	4	1		1	6	4	10
ARKANSAS		15	1	24	1	9		1	7	49	9	58
Arkansas Agricultural and Mechanical College Jonesboro	C			2						2		2
Arkansas Baptist College † Little Rock									1		1	1
Arkansas Polytechnic Institute * Russellville				2						2		2
Arkansas State Normal School Conway		1								1		1
Galloway Woman's College Searcey									1		1	1
Hendrix College Conway	C	6		2		2			3	10	3	13
Jonesboro Junior College * Jonesboro				2						2		2
Little Rock Junior College * Little Rock	C	1		4						5		5
Ouachita College Arkadelphia	C	1				1			2	5	2	7
St John's Seminary Little Rock		1								1		1
University of Arkansas Fayetteville	A-C	5	1	9	1	6		1		21	2	23
CALIFORNIA		91	5	86	17	91	10	16	53	294	85	378
California College of Pharmacy San Francisco					1		1				2	2
Chaffey Junior College * Ontario				1		1				2		2
Chico Junior College * Chico				1						1		1
College of the Pacific Stockton	A			1		1			1	2	1	3
Fresno State Teachers College Fresno		4		5						9		9
La Verne College La Verne									1		1	1
Loyola College Los Angeles		1		2					1	3	1	4
Mills College Oakland	A						1				1	1
Notre Dame Academy Salinas				1						1		1
Occidental College Los Angeles	A	3			1	1			1	4	2	6
Pacific Union College Angwin		8		25		6			1	39	1	40
*Pasadena Junior College * Pasadena*		1		1						2		2
Pomona College Claremont	A	3							4	3	4	7
Riverside Junior College * Riverside		2								2		2
Salinas Junior College * Salinas		1								1		1
San Bernardino Junior College * San Bernardino				2						2		2
San Jose State Teachers College San Jose				4						4		4
Santa Barbara Collegiate School Santa Barbara				1						1		1
San Mateo Collegiate School San Mateo		4		3						7		7
Santa Ana Junior College * Santa Ana				1						1		1
Santa Clara College Santa Clara		1		2						3		3
Santa Rosa Junior College * Santa Rosa				2						2		2
St Ignatius College San Francisco		6	2	2		2				10	2	12
St Mary's College St Mary's College	W			1		1			1	2	1	3
Sacramento Junior College * Sacramento		2		3						5		5
Stanford University Palo Alto	A	25	2	6	9	10	5	5	17	[illegible]	33	88
State Teachers College San Diego	W			4		1			1	5	1	6
University of California Berkeley-Los Angeles	A	10	1	20	2	48	1	11	15	104	19	123
University of Redlands Redlands	A-W	1		1						2		2
University of Southern California Los Angeles	A	10		1	4	10	2		8	21	14	35
Whittier College Whittier	A					1			2	1	2	3
COLORADO		23		15	1	17		3	10	63	11	74
Colorado Agricultural College, Fort Collins	C	1		2					3	3	3	6
Colorado College Colorado Springs	A-C	1		1		4			1	6	1	7
Colorado School of Mines Golden	C								1		1	1
Grand Junction Junior College * Grand Junction		3								3		3
Regis College * Denver	C					1			1	1	1	2
University of Colorado Boulder	A-C	13		10	1	10		2	1	35	2	37
University of Denver Denver	C	10		2		2		1	3	15	3	18
CONNECTICUT		6		6		10	7	2	43	24	55	79
Connecticut Agricultural College Storrs		3		1						4		4
Connecticut College for Women New London	A								2		2	2
Trinity College Hartford	A			1			1		3	1	4	5
Wesleyan University Middletown	A			1		1	3		5	2	8	10
Yale University New Haven	A	3		3		9	3	2	33	17	41	58
DELAWARE		1		1				1	7	3	7	10
University of Delaware Newark	A-M	1		1				1	7	3	7	10
DISTRICT OF COLUMBIA		65	8	82	7	20	5	8	35	176	55	231
American University Washington	M	1			1				2	1	3	4
Catholic University of America Washington	A-M	4		1	1	2			6	7	7	14
Georgetown University Washington	A-M	30		41	2		2	1	10	72	14	86
George Washington University Washington	M	23	8	27	2	12	1	4	4	64	15	79
Howard University † Washington	M	4		5	1	5	2	3	11	17	14	31
Washington Missionary College Takoma Park		3	1	10		1			2	14	3	17
FLORIDA		6		16		6	1	2	10	30	11	41
Florida A and M College † Tallahassee						1				1		1
Florida State College for Women Tallahassee	A-S			1						1		1
John B Stetson University DeLand		2		1		1	1		1	4	2	6
University of Florida Gainesville	A-S	4		14		4		2	9	24	9	33
GEORGIA		30	2	30	2	23	3		29	83	36	119
Agnes Scott College Decatur	A-S								2		2	2
Andrew College * Cuthbert	S	1								1		1
Atlanta College of Pharmacy Atlanta		1			1					1	1	2
Atlanta University † Atlanta									3		3	3

* Junior colleges † Negro colleges

TABLE A.—Sources of Premedical Education First Year Students 1929-1930—Continued

NAME OF COLLEGE	Accredited Agencies Approving	1 Year		2 Years		3 Years		4 Years		Totals*		Grand Total
		No Degree	Degree	No Degree	Degree	No Degree	Degree	No Degree	Degree	No Degree	Degree	
GEORGIA—Continued												
Brenau College Gainesville		1								1		1
Clark University † Atlanta									1		1	1
Emory University Atlanta	A-S	10		12	1	1			8	23	9	32
Fairmount College Fairmount		1								1		1
Georgia School of Technology Atlanta	S	3		1					1	4	1	5
Junior College of Augusta * Augusta	S	2		2						4		4
Mercer University Macon	S	1		3		5	2		2	9	4	13
Morehouse College † Atlanta		1							3	1	3	4
Oglethorpe University Atlanta			1	1					3	1	4	5
University of Georgia Athens	A-S	8	1	10		3	1		6	21	8	29
Wesleyan College Macon	S	1								1		1
Young Harris College * Young Harris				1						1		1
IDAHO		6		2		1		1	2	10	2	12
College of Idaho Caldwell	W	1								1		1
Idaho Technical Institute Moscow		1								1		1
Northwest Nazarene College * Nampa		1								1		1
Ricks College * Rexburg		1								1		1
University of Idaho Moscow	A-W	2		2		1		1	2	6	2	8
ILLINOIS		236	14	204	32	43	11	2	62	480	119	599
Armour Institute of Technology Chicago	C	1							1	1	1	2
Augustana College and Theological Seminary Rock Island	C	2								2		2
Aurora College Aurora		1								1		1
Bradley Polytechnic Institute Peoria	C			2		1				3		3
Broadview College * LaGrange		2	1	2		1				5	1	6
Carthage College Carthage	A-C			1		2			2	3	2	5
Central Y M C A College * Chicago	C	14		2		1	1			17	1	18
Crane Junior College * Chicago	C	64		69	8	7	1		1	140	10	150
DePaul University Chicago	C	5		2					3	7	3	10
Eastern Illinois State Teachers College Charleston	C	3								3		3
Elgin Junior College * Elgin				1						1		1
Elmhurst College * Elmhurst	C	2				1				3		3
Eureka College Eureka	A-C			1						1		1
Greenville College Greenville				1						1		1
Illinois College Jacksonville	A-C			3					1	3	1	4
Illinois Wesleyan University Bloomington	A-C	2		2		1			2	5	2	7
Illinois Woman's College Jacksonville	A-C	1								1		1
James Millikin University Decatur	C	1		3				1	1	5	1	6
Joliet Junior College * Joliet	C	2		2						4		4
Knox College Galesburg	A-C					1	1		2	1	3	4
Lake Forest College, Lake Forest	A-C	2								2		2
LaSalle-Peru Oglesby Junior College * LaSalle	C				1	1				1	1	2
Lewis Institute Chicago	C	25	1	9		2	1		2	36	4	40
Loyola University, Chicago	C	8	1	23	2	1			1	32	4	36
McKendree College Lebanon		1								1		1
Monmouth College Monmouth	A-C					1	1		4	1	5	6
Morton Junior College * Cicero	C	2		4						6		6
North Central College Naperville	A-C			1		1			4	2	4	6
Northwestern University Evanston	A-C	29	1	14	6	13	1		3	56	11	67
Northwestern University Dental School Chicago		1	1						2	1	3	4
Northwestern University School of Pharmacy Chicago				1						1		1
Rockford College Rockford	A-C								1		1	1
Rosary College River Forest	A-C	1								1		1
Shurtleff College Alton	C								1		1	1
Southern Illinois State Teachers College Carbondale						1			1	1	1	2
St. Bede's College Peru		1								1		1
St. Procopius College, Lisle				1		3				4		4
St Viator's College Bourbonnais		1								1		1
University of Chicago Chicago	A-C	18	8	10	9	1	3	1	16	30	36	66
University of Illinois, Urbana	A-C	56	1	47	6	9	1		12	112	20	132
University of Illinois College of Pharmacy Chicago							1				1	1
University of Illinois Dental School Chicago				1						1		1
Western Illinois State Teachers College Macomb	C	1								1		1
Wheaton College Wheaton	C			2					2	2	2	4
INDIANA		48		73	6	27	9	6	56	155	71	226
Ball State Teachers College Muncie		1								1		1
Butler University Indianapolis	C	5		3	1	1	1	1	4	12	6	18
DePauw University Greencastle	A-C			2		2	1		6	4	7	11
Earlham College Richmond	A-C	1				1			4	2	4	6
Evansville College Evansville		1		2					1	3	1	4
Franklin College Franklin	A-C				1						1	1
Goshen College Goshen							1		3		4	4
Hanover College Hanover	C			1					2	1	2	3
Huntington College * Huntington								1		1		1
Indiana Central College Indianapolis		1								1		1
Indiana State Teachers College Terre Haute		1				1			6	2	6	8
Indiana University Bloomington	A-C	25		48		3	1	2	7	84	8	92
Indianapolis College of Pharmacy Indianapolis					1						1	1
Manchester College North Manchester				2					1	2	1	
Oakland City College Oakland City					1						1	1
Purdue University Lafayette	A-C	3		3		4	3		2	10	5	15
St Mary's College Notre Dame	C	1								1		1
Taylor University Upland					1				1		2	2
Union Christian College Merom				1						1		1
Valparaiso University Valparaiso	C	1		3	1					3	1	4
Vincennes University * Vincennes		1								1		1
University of Notre Dame South Bend	A-C	8		9		-	-	2	16	27	18	45
Wabash College Crawfordsville	A-C								3		3	3
IOWA		77	3	74	2	37	7	3	20	191	32	223
Buena Vista College Storm Lake				1			2			1	-	3
Central College Pella				1						1		1
Coe College Cedar Rapids	A-C	1		3		1			1	5	1	6
Columbia College Dubuque	A-C	2		3		2			1	7	1	8
Cornell College Mount Vernon	A-C			1		1				2		2
Des Moines University Des Moines		2		2		1			1	5	1	6
Drake University Des Moines	A-C	3		5		7			2	15	2	17
Dubuque University Theological Seminary Dubuque		1								1		1

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* Junior colleges. † Negro colleges.

TABLE A.—*Sources of Premedical Education, First Year Students 1929-1930—Continued*

Name of College	Accredited Agencies Approving	1 Year		2 Years		3 Years		4 Years		Totals		Grand Total
		No Degree	Degree	No Degree	Degree	No Degree	Degree	No Degree	Degree	No Degree	Degree	
IOWA—Continued												
Estherville Junior College* Estherville				1						1		1
Ft Dodge Junior College Ft Dodge		1		2								3
Graceland College* Lamoni	O			2						2		2
Grandview College Des Moines		1								1		1
Grinnell College Grinnell	A-C	2		3			1	1	2	6	3	9
Iowa State College of Agriculture and Mechanical Arts Ames	A-C	1				1				2		2
Iowa State Teachers College Cedar Falls		1		1		2				4		4
Iowa Wesleyan College Mt Pleasant	O	1								1		1
John Fletcher College Oskaloosa							1				1	1
Luther College Decorah	O	1								1	3	4
Morningside College Sioux City	A-O	1		1		2	1	1		5	1	6
Parsons College Fairfield	O			1		1				2		2
Penn College Oskaloosa	C	2			1	1			2	3	3	6
Simpson College Indianola	A-O	1								1		1
St Ambrose College Davenport	C					1			1	1	1	2
State University of Iowa Iowa City	A-C	53	3	44	1	17	2	1	4	115	10	125
University of Dubuque Dubuque	C	1							1	1	1	2
University of Iowa College of Pharmacy Iowa City									1		1	1
Waldorf Junior College* Forest City		1		1						2		2
Wartburg College Clinton		1		1					1	2	1	3
Western Union College LeMars				1						1		1
KANSAS		35	1	27	3	22	6	2	29	86	39	125
Arkansas City Junior College Arkansas City				1						1		1
Baker University Baldwin City	A-C			3			1		1	3	2	5
Bethany College Lindsborg						1				1		1
Caney College Caney				1						1		1
College of Emporia Emporia	C	1				1			1	2	1	3
Friends University Wichita	O	2					1		1	2	2	4
Garden City Junior College Garden City				1						1		1
Independence Junior College Independence				1						1		1
Iola Junior College* Iola		1								1		1
Kansas City Junior College* Kansas City				1						1		1
Kansas City University Kansas City		1								1		1
Kansas State Agricultural College Manhattan	A-O	1				1			2	2	2	4
Kansas State Teachers College of Emporia	C								1		1	1
Kansas State Teachers College Pittsburg		2			1	1					1	4
Kansas Wesleyan University Salina		1							1	1	1	2
Municipal University of Wichita	O					1				1	3	4
Ottawa University Ottawa	C	1				1				2		2
St Benedict's College Atchinson	O	1								1		1
St Mary's College* St Mary's	C	2								7	3	10
Southwestern College Winfield	C	1		1					2	2	2	4
Sterling College Sterling	C	1								1		1
University of Kansas Lawrence	A-O	18	1	11	2	16	1	2	14	47	18	65
Washburn College Topeka	A-O	2		2					2	4	2	6
Western University Quindaro									1		1	1
KENTUCKY		32	5	33	4	23	12	1	17	89	38	127
Asbury College Wilmore		1		1		1	1		1	3	2	5
Berea College Berea	A-S					1			1	1	1	2
Bethel Woman's College* Hopkinsville	S	1		2	1						1	4
Bowling Green College Bowling Green		2								2		2
Centre College Danville	A-S	1					2		2	1	4	5
Cumberland Junior College* Williamsburg		2								2		2
Georgetown College Georgetown	S					1	2		2	1	4	5
Kentucky State Teachers College Bowling Green	S	7	1	1			1		1	8	3	11
Kentucky State Teachers College Richmond	S			1	2		1			1	3	4
Kentucky Wesleyan University Winchester									1		1	1
Lindsey Wilson Junior College* Columbia				1						1		1
Louisville College of Pharmacy Louisville				1						1		1
Murray State Teachers College Murray	S			1			1		1	1	2	3
Ogden College Bowling Green				1						1		1
Transylvania University Lexington	S	2							1	2	4	6
University of Kentucky Lexington	A-S	4	2		1	6	1	1	6	16	10	26
University of Louisville Louisville	S	11	2	18		14			1	43	3	46
Union College Barbourville		1		1						2		2
LOUISIANA		29		35	1	14	6		14	78	21	99
Centenary College Shreveport	S	2		1					2		2	5
Jefferson College Convent		1								1		1
Leland University New Orleans									1		1	1
Louisiana College Pineville	S	2					2			2	5	7
Louisiana Polytechnic Institute Ruston	S	1				2	2			3	2	5
Louisiana State University Baton Rouge	A-S			5		2	2		4	7	6	13
Loyola University New Orleans		1				1			1	2	1	3
Newcomb Memorial College New Orleans	A-S								1		1	1
Southwestern Louisiana Institute Lafayette	S	1		1		1				3		3
Tulane University of Louisiana New Orleans	A-S	21		28	1	8			2	57		60
MAINE		1		1	2	2	2	1	14	5	18	23
Bates College Lewiston	A-N								5		5	5
Bowdoin College Brunswick	A-N	1			1				5	1	6	7
Colby College Waterville	A-N			1		1	1		3	2	4	6
University of Maine Orono	A-N				1	1	1	1	1	2	3	5
MARYLAND		12	1	15	5	12	25	1	43	40	74	114
College of Notre Dame Baltimore	M	1								1		1
Goucher College Baltimore	A-M-S			1					4	1	4	5
Hood College Frederick	M								1		1	1
Johns Hopkins University Baltimore	A-M-S	4	1	3	2		4	1	16	8	23	31
Loyola College Baltimore				1					3	1	3	4
Morgan College† Baltimore	M			1			1		2	1	3	4
Mt. St Mary's College Emmitsburg	M			2					2	2	2	4
St John's College Annapolis	M	1							7	1	7	8
University of Maryland College Park	A-M	4		4	2	12	5		3	20	10	30
University of Maryland School of Pharmacy Baltimore		2			1		15			2	16	18
Washington College Chestertown	M								2		2	2
Western Maryland College Westminster	M			3					3	3	3	6

* Junior colleges † Negro colleges

TABLE A.—*Sources of Premedical Education, First Year Students, 1929-1930—Continued*

NAME OF COLLEGE	Accredited Agencies Approving	1 Year		2 Years		3 Years		4 Years		Totals		Grand Total
		No Degree	Degree	No Degree	Degree	No Degree	Degree	No Degree	Degree	No Degree	Degree	
MASSACHUSETTS		50	1	92	19	38	12		146	180	178	358
Amherst College, Amherst	A-N	1		2	2	2			8	5	10	15
Assumption College, Worcester		1					1		4	1	5	6
Atlantic Union College,* South Lancaster		2		4						6		6
Boston College, Chestnut Hill	A	1		2	2				9	3	11	11
Boston University, Boston	A-N	6		5	6	6			9	17	15	32
Clark University, Worcester	A-N	4					1		1	4	2	6
Harvard University, Cambridge	A-N	8			9	2	5		52	10	66	76
Holy Cross College, Worcester	N	1		4		1			19	6	22	28
International Y. M. C. A. College, Springfield			1								1	1
Massachusetts Agricultural College, Amherst	A			1						1		1
Massachusetts Institute of Technology, Cambridge	A-N			1					2	4	2	6
Mt. Holyoke College, South Hadley	A-N			1			1		4	1	5	6
Northeastern University, Boston									1		1	1
Radcliffe College, Cambridge	A-N	1				1			3	2	3	5
Simmons College, Boston	A-N	2								2		2
Smith College, Northampton	A-N								7		7	7
Tufts College, Medford	A-N	20		63		28			9	111	9	120
Wellesley College, Wellesley	A-N	1		1		1			7	3	7	10
Wheaton College, Norton	A-N	1							2	1	2	3
Williams College, Williamstown	A-N					2	1		9	2	10	12
Worcester Polytechnic Institute, Worcester	A	1								1		1
MICHIGAN		61	8	84	19	83	15	10	93	223	135	358
Albion College, Albion	A-C			1	2	7	2		2	8	6	14
Alma College, Alma	C								2		2	2
Battle Creek Junior College,* Battle Creek	C			1		1				2		2
Bay City Junior College,* Bay City	C			3		1				4		4
Calvin College, Grand Rapids						2		1	6	3	6	9
College of the City of Detroit	C	19	2		2	24			17	43	21	64
Emanuel Missionary College,* Berrien Springs	C	5	1	6	1	4	1		2	15	5	20
Ferris Institute, Big Rapids		1		2						3		3
Flint Junior College,* Flint	C	1		1						2		2
Grand Rapids Junior College,* Grand Rapids	C	2										7
Highland Park Junior College,* Highland Park	C	1		4					1	5		6
Hillsdale College, Hillsdale	C					2			4	2	4	6
Hope College, Holland	C	1				2			5	3	5	8
Kalamazoo College, Kalamazoo	A-C								1		1	1
Michigan Coll. of Agric. and Applied Science, East Lansing	C	4	1	5		4			3	13	4	17
Michigan College of Mining and Technology, Houghton	C	1								1		1
Michigan State Normal College, Ypsilanti	C	2		1				2	1	5	2	7
Muskegon Junior College,* Muskegon	C			1						1		1
Olivet College, Olivet				2					2	2	2	4
Pontiac Junior College,* Pontiac		1								1		1
Port Huron Junior College,* Port Huron				1						1		1
St. Marys College, Orchard Lake				1		1				2		2
State Teachers College (Western), Kalamazoo	C				1	1			2	1	3	4
State Teachers College (Northern), Marquette	C	1								1		1
State Teachers College (Central), Mt. Pleasant	C							1		1		1
University of Detroit		2		7	1	6	[illegible]		[illegible]	15	6	21
University of Michigan, Ann Arbor	A-C	31	4	20	12	30	10		42	81	68	149
MINNESOTA		45		76	5	75	3	6	21	202	29	231
Carleton College, Northfield	A-C			5					3	5	3	8
College of St. Thomas, St. Paul	C	1		11					1	15	1	16
Concordia College, Moorhead	C			2					2	2	2	4
Duluth Junior College,* Duluth				2						2		2
Gustavus Adolphus College, St. Peter	C	1			1		1		2	1	4	5
Hamline University, St. Paul	A-C			1	1				1	1	2	3
Hibbing Junior College,* Hibbing	C			2		1				3		3
Hutchinson Theological Seminary, Hutchinson						1				1		1
Itasca Junior College,* Coleraine		1								1		1
Macalester College, St. Paul	A-C			1					2	4	2	6
Northwest College, Fergus Falls		1								1		1
Rochester Junior College,* Rochester	C	2								2		2
St. John's University, Collegeville		2		1		2				5		5
St. Mary's College, Winona				1		1	1			2	1	
St. Olaf's College, Northfield	C	1		2		2	1		5	5	6	11
State Teachers College, Mankato				1						1		1
University of Minnesota, Minneapolis	A-C	[illegible]		46		[illegible]		6	[illegible]	[illegible]	[illegible]	[illegible]
Virginia Junior College,* Virginia	C			1						1		1
MISSISSIPPI		13	2	28		7	3		11	43	16	64
Alcorn A. and M. College for Negroes,† Alcorn									1		1	1
Blue Mountain College, Blue Mountain	S	1								1		1
Chickasaw College,* Pontotoc				1						1		1
Gulf Park College,* Gulfport	S	1								1		1
Millsaps College, Jackson	S	2				2			1	4	1	5
Mississippi A. and M. College, Starkville	S			4						[illegible]		7
Mississippi College, Clinton	S					1	[illegible]		6	1	9	10
Mississippi State College for Women, Columbus	S			1						1		1
Pearl River College,* Poplarville						1				1		1
Rust College,† Holly Springs									2		2	2
State Teachers College, Hattiesburg	S		1								1	1
University of Mississippi, University	A-S		1	22		[illegible]			1	30	2	[illegible]
Whitworth College, Brookhaven	S	1								1		1
MISSOURI		63	4	63	13	42	8	6	33	174	58	232
Central College,* Fayette	A-C	1		5					2	9	2	11
Christian College, Columbia	C				1						1	1
Clinton Theological Seminary, Clinton				1						1		1
Culver-Stockton College, Canton	C			1						1		1
Concordia Theological Seminary, St. Louis				1						1		1
Drury College, Springfield	A-C	1							1	1		2
Junior College of Kansas City	C	7		11	6	2				20	6	26
Kemper Military School, Boonville	C	1		1						2		2
Missouri School of Mines, Rolla							1				1	1
Missouri State Teachers College (Northeast), Kirksville	C	2	1	2		2				6	1	7
Missouri State Teachers College (Northwest), Maryville	C						1				1	1
Missouri State Teachers College (Southwest), Springfield	C			1					1	4	1	5
Missouri State Teachers College (Central), Warrensburg	C	2							2	2	2	4
Missouri Valley College, Marshall	C				1	1			1	1	2	3
Park College, Parkville	A-C	2		2			[illegible]		[illegible]	4	8	12

* Junior colleges. † Negro colleges.

TABLE A.—*Sources of Premedical Education First Year Students, 1929-1930—Continued*

NAME OF COLLEGE	Accredited Agencies Approving	1 Year No Degree	1 Year Degree	2 Years No Degree	2 Years Degree	3 Years No Degree	3 Years Degree	4 Years No Degree	4 Years Degree	Totals No Degree	Totals Degree	Grand Total
MISSOURI—Continued												
Rockhurst College, Kansas City				3						3		3
St. Joseph Junior College*, St. Joseph	C	1		4						5		5
St. Louis College of Pharmacy, St. Louis		1								1		1
St. Louis University, St. Louis	C	14	1	17		6		1	2	38	3	41
Southwest Baptist Junior College*, Bolivar					1						1	1
Tarkio College, Tarkio	C								1		1	1
University of Missouri, Columbia	A-C-S	18		6	2	17	1	5	3	46	6	52
Washington University, St. Louis	A-C	8	2	5	1	8			14	21	17	38
Wentworth Junior College*, Lexington				1						1		1
Wesleyan College, Cameron							1				1	1
Westminster College, Fulton	A-C	1				1	1			2	1	3
William Jewell College, Liberty	A-O	1			1	2			1	3	2	5
William Woods College*, Fulton	C			2						2		2
MONTANA		6		12	1	1	1		4	19	6	25
Intermountain Union College, Helena	C-W						1				1	1
Montana State College, Bozeman	C-W	1		2					2	3	2	5
Montana State School of Mines, Butte		3		1						4		4
Mount St. Charles College*, Helena	C	1		4	1					5	1	6
University of Montana, Missoula	A-C	1		4		1			2	6	2	8
University of Montana School of Pharmacy, Missoula				1						1		1
NEBRASKA		42	1	85	4	27	3	5	24	159	32	191
Cotner College, Bethany				1					1	1	1	2
Creighton Dental College, Omaha						1				1		1
Creighton School of Pharmacy, Omaha									2		2	2
Creighton University, Omaha	C	6		4		12	1		2	52	3	55
Dana College, Blair				2						2		2
Doane College, Crete	A-C	1								1		1
Grand Island College, Grand Island				2					2	2	2	4
Hastings College, Hastings	C	1						1	1	2	1	3
Hebron Junior College*, Hebron		1								1		1
Kearney State Teachers College, Kearney		1								1		1
Luther Junior College*, Wahoo		1								1		1
Midland College, Fremont									1		1	1
Nebraska Wesleyan University, Lincoln	C	2		5		1			5	8	5	13
State Teachers College, Chadron				2						2		2
State Teachers College, Peru		1								1		1
State Teachers College, Wayne		1							1	1	1	2
Union College*, College View	C	2		4	1	1	1		3	7	5	12
University of Nebraska, Lincoln	A-C	18	1	24	3	11	1	4	6	57	11	65
University of Omaha, Omaha		6		8						14		14
York College, York		1		3		1				5		5
NEVADA									2		2	2
University of Nevada, Reno	A								2		2	2
NEW HAMPSHIRE		5		5	2	16	1	2	32	28	35	63
Dartmouth College, Hanover	A-N	3		3		15	1	2	25	23	26	49
St. Anselm's College, Manchester		1								1		1
University of New Hampshire, Durham	A-N	1		2	2	1			7	4	9	13
NEW JERSEY		7	1	9		4	2	2	43	22	45	68
Bloomfield Theological Seminary, Bloomfield		1								1		1
Georgian Court College, Lakewood	M	1								1		1
Newark Junior College*, Newark		1								1		1
New Jersey College for Women, New Brunswick							1				1	1
New Jersey College of Pharmacy, Newark		1								1		1
Princeton University, Princeton	A-M	2				2		1	28	5	28	33
Rutgers University, New Brunswick	A-M	1		5		2	1	1	15	9	16	25
Seton Hall College, South Orange				3						3		3
Trenton Junior College*, Trenton				1						1		1
Upsala College, Kenilworth			1								1	1
NEW MEXICO		3		2					1	5	1	6
New Mexico Coll. of Agric. and Mechanic Arts, State College	C	1								1		1
New Mexico Military Institute*, Roswell		1		2						3		3
State University of New Mexico, Albuquerque	C	1							1	1	1	2
NEW YORK		143	3	167	17	220	38	14	417	544	475	1 018
Alfred University, Alfred	A-M	3		2		3	1		5	8	6	14
Barnard College, New York	A-M	2			1				3	2	4	6
Canisius College, Buffalo	M	5	1	15		4			10	24	11	35
Colgate University, Hamilton	A-M	1		1		3	1		15	5	16	21
College of the City of New York	A-M	21		7	1	6	6	2	61	36	68	104
College of St. Bonaventure, Alleghany	M	2		4		4			3	10	3	13
Columbia University, New York	A-M	30		41	2	33	5	4	49	108	56	164
Columbia University Nurses School, New York							1				1	1
Concordia College Institute, Bronxville				1						1		1
Cooper Union Junior College*, New York									1		1	1
Cornell University, Ithaca	A-M	5		5	2	19	10	1	34	30	46	76
D'Youville College, Buffalo	M	1								1		1
Elmira College, Elmira	A-M			1		2				3		3
Fordham University, New York	A-M	1	1	6	1	8		1	68	16	70	86
Hamilton College, Clinton	A-M	1				1		1	7	3	7	10
Houghton College, Houghton		2							2	2	2	4
Hobart College, Geneva	A-M	2							1	2	1	3
Hunter College, New York	A-M	4				4			7	8	7	15
Long Island College, Brooklyn		1								1		1
Manhattan College, New York	M			1	1	1			13	2	14	16
New York State College of Agriculture, Ithaca		1								1		1
New York State Teachers College, Albany	A								3		3	3
New York University, New York	A-M	28		41	2	60	3	3	71	132	76	208
Niagara University, Niagara Falls	M	1		1		1			1	3	1	4
Polytechnic Institute of Brooklyn	A-M	2								2		2
Rensselaer Polytechnic Institute, Troy	A-M					2				2		2
Russell Sage College, Troy	M						1				1	1
St. Bernard's Seminary, Rochester						1				1		1
St. Francis College, Brooklyn		4	1	4	1	3	1		1	11	4	15
St. John's College, Brooklyn	M	4			3	7	3		16	11	22	33
St. Lawrence University, Canton	A-M					2			3	2	3	5

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* Junior colleges. † Negro colleges.

TABLE A.—*Sources of Premedical Education First Year Students 1929-1930—Continued*

NAME OF COLLEGE	Accredited Agencies Approving	1 Year		2 Years		3 Years		4 Years		Totals		Grand Total
		No Degree	Degree	No Degree	Degree	No Degree	Degree	No Degree	Degree	No Degree	Degree	
NEW YORK—Continued												
St Stephens College Annandale-on Hudson	A-M						1				1	1
Syracuse University Syracuse	A-M	8		12	1	20	3	2	15	42	19	61
Union College Schenectady	A-M					12			12	12	12	24
United States Military Academy West Point	A	1		1						2		2
University of Buffalo	A-M	9		24	1	21			2	54	3	57
University of Buffalo School of Pharmacy Buffalo					1		1				2	2
University of Buffalo School of Dentistry Buffalo									1		1	1
University of Rochester	A-M	3				3	1		6	6	7	13
Vassar College Poughkeepsie	A-M	1							4	1	4	5
NORTH CAROLINA		**17**	**2**	**14**	**4**	**24**	**6**	**1**	**58**	**56**	**70**	**126**
Agricultural and Technical College † Greensboro							2				2	2
Catawba College Salisbury	S								1		1	1
Davidson College Davidson	A-S			2			1		12	2	13	15
Duke University Durham	A-S	4	1		1	2	1		13	6	16	22
Flora MacDonald College Red Springs									1		1	1
Guilford College Guilford College	S				1						1	1
High Point College High Point									2		2	2
Johnson C Smith College † Charlotte									1		1	1
Lenoir Rhyne College Hickory	S					1				1		1
Livingstone College † Salisbury									1		1	1
Mars Hill College * Mars Hill	S			1	1					1	1	2
Meredith College, Raleigh	A-S	1								1		1
North Carolina College for Women Greensboro	S	1								1		1
North Carolina State College of A. and E West Raleigh	S			1					1	1	1	2
Rutherford College * Rutherford				1						1		1
Shaw University † Raleigh									4		4	4
University of North Carolina Chapel Hill	A-S	8	1	6	1	10	1	1	12	25	15	40
Wake Forest College Wake Forest	S	2		2		11	1		10	15	11	26
Weaver College * Weaverville				1						1		1
Wingate Junior College * Wingate		1								1		1
NORTH DAKOTA		**6**	**1**	**10**	**1**	**14**			**6**	**30**	**8**	**38**
Dickinson State Normal Dickinson				3						3		3
Jamestown College Jamestown	C								4		4	4
North Dakota Agricultural College Fargo	C	1	1	2	1	1				4	2	6
State Teachers College Minot				1		1				2		2
University of North Dakota Grand Forks	A-C	5		4		12			2	21	2	23
OHIO		**78**	**7**	**87**	**16**	**106**	**30**	**14**	**137**	**285**	**190**	**475**
Antioch College Yellow Springs	C	1						1		2		2
Ashland College Ashland						1			2	1	2	3
Baldwin Wallace College Berea	C	2			1	2	1		1	4	3	7
Bluffton College, Bluffton		1								1		1
Capital University Columbus	C	1		1	1	2			2	4	3	7
Case School of Applied Science Cleveland	A-C	2							1	2	1	3
Cedarville College Cedarville				1					5	1	5	6
College of Wooster Wooster	A-C	2				2			4	4	4	8
Defiance College Defiance									1		1	1
Denison University Granville	A-C	4		3		4	1		2	11	3	14
Heidelberg College Tiffin	A-C						1		4		5	5
Hiram College Hiram	A-C			1		2		1		4		4
John Carroll University Cleveland	C	3		1		3	1		5	7	6	13
Kent Junior College * Kent		2								2		2
Kent State Normal Kent		2								2		2
Kenyon College Gambier	A-C			2	1	1			4	3	5	8
Lake Erie College Painesville	A-C	1					1			1	1	2
Marietta College Marietta	A-C			1		4			2	5	2	7
Miami University Oxford	A-C	6		3	1	7	1	2	2	18	4	22
Mt Union College Alliance	A-C				2	1			5	1	7	8
Muskingum College New Concord	C	1							4	1	4	5
Oberlin College Oberlin	A-C	3	1	3	1	2	2		10	8	14	22
Ohio Northern University Ada									2		2	2
Ohio State University Columbus	A-C	29	4	22	6	29	9	3	26	83	45	128
Ohio University Athens	A-C	3		2	1	1			2	6	3	9
Ohio Wesleyan University Delaware	A-C	1		1		2	2		10	4	12	16
Otterbein College Westerville	A-C						1				1	1
St John's Academy Toledo		1					1		1	1	2	3
St Xavier College Cincinnati	C					6			3	6	3	9
University of Akron Akron	A-C	1		2		3		1	7	7	7	14
University of Cincinnati	A-C	4		29		13		3	3	49	3	52
University of Dayton Dayton	C			2		2			1	4	1	5
University of the City of Toledo	C		2	2		4	4		2	6	8	14
Western College for Women Oxford	A-C					1		1		2		2
Western Reserve University Cleveland	A-C	4		7	1	13	3	1	24	25	28	53
Wilberforce University † Wilberforce					1			1	2	1	3	4
Wittenberg College Springfield	A-C	4		4		1	2			9	2	11
OKLAHOMA		**29**	**1**	**39**	**1**	**17**	**6**	**1**	**15**	**86**	**23**	**109**
East Central State Teachers College, Ada		1		2					1	3	1	4
Lawton Junior College * Lawton		1								1		1
Northeast State Teachers College Tahlequah						1			2	1	2	3
Northwestern Academy Carrier		1								1		1
Northwestern State Teachers College Alva									2		2	2
Oklahoma Agricultural and Mechanical College Stillwater	C	4		2					1	6	1	7
Oklahoma Christian Junior College * Cordell		1								1		1
Oklahoma City University		1		1		3				5		5
Oklahoma College for Women Chickasha	C								1		1	1
Oklahoma Baptist College Shawnee		1		4					2	5	2	7
Phillips University Enid	C			1		1				2		2
Southeastern State Teachers College Durant									1		1	1
Southwestern State Teachers College Weatherford		2		3					1	5	1	6
University of Oklahoma Norman	A-C	16		26	1	12	5	1	4	55	10	65
University of Oklahoma College of Pharmacy Norman							1				1	1
University of Tulsa	C	1	1							1	1	2
OREGON		**11**		**13**	**3**	**21**	**1**	**5**	**17**	**50**	**21**	**71**
Albany College Albany		1								1		1
Columbia University Portland						1				1		1
Linfield College McMinnville	W								2		2	2

* Junior colleges † Negro colleges

TABLE A.—*Sources of Premedical Education, First Year Students, 1929-1930—Continued*

NAME OF COLLEGE	Accredited Agencies Approving	1 Year		2 Years		3 Years		4 Years		Totals		Grand Total
		No Degree	Degree	No Degree	Degree	No Degree	Degree	No Degree	Degree	No Degree	Degree	
OREGON—Continued												
Northern Pacific College, Newberg				1						1		1
Oregon Agricultural College, Corvallis	A-W								1		1	1
Oregon State Normal, Monmouth	W	2				3		1		6	3	9
Reed College, Portland	A-W	2		3	1				1	5	2	7
St. Mary's College, Portland				1						1		1
University of Oregon, Eugene	A-W	6		8	2	16	1	4	7	34	10	44
Willamette University, Salem	A-W					1			3	1	3	4
PENNSYLVANIA		107	12	201	23	142	42	20	260	470	337	807
Academy of the New Church, Bryn Athyn		1								1		1
Albright College, Myerstown	M	2		1	1			1	6	4	7	11
Allegheny College, Meadville	A-M	4	1	2		1			8	7	9	16
Bryn Mawr College, Bryn Mawr	A-M								1		1	1
Bucknell University, Lewisburg	A-M	3		1		1		4	12	12	12	24
Carnegie Institute of Technology, Pittsburgh	A-M	1								1		1
Dickinson College, Carlisle	A-M	1		1	1	2			6	4	7	11
Duquesne University, Pittsburgh		3	1	1		7	1			11	2	13
Elizabeth College, Elizabethtown				1					2	1	2	
Franklin and Marshall College, Lancaster	A-M	1	[illegible]	2	3	[illegible]	1		6	5	11	18
Geneva College, Beaver Falls	M	5				1	1		7	6	8	14
Gettysburg College, Gettysburg	A-M	1		1		1			6	3	6	9
Grove City College, Grove City		2							3	2	3	5
Hahnemann College of Science, Philadelphia		9		71	1			1		81	1	82
Haverford College, Haverford	A-M					1			7	1	7	8
Juniata College, Huntingdon	M			1		1			1	2	1	3
Lafayette College, Easton	A-M	3	1	2	1	1	1	1	13	7	16	23
LaSalle College, Philadelphia		2		1		2				5		5
LaSalle College of Pharmacy, Philadelphia		1								1		1
Lebanon Valley College, Annville	M	1		1	1				2	2	3	5
Lehigh University, South Bethlehem	A-M	1		3				1	7	5	7	12
Lincoln University,† Lincoln University	M		2		1		1		18		22	22
Moravian College, Bethlehem	M	1			1				4	1	5	6
Muhlenberg College, Allentown	A-M	6		1						7		7
Pennsylvania State College, State College	A-M	8		6		25		1	13	40	13	53
Philadelphia College of Pharmacy				1	2					1	2	3
Philadelphia Normal School, Philadelphia				1						1		1
Pittsburgh College of Pharmacy, Pittsburgh				1						1		1
Polish National Alliance College, Cambridge Springs				1						1		1
St. Francis College, Loretto					1		2				3	3
St. Joseph's College, Philadelphia	M	1	1	1		1			8	3	9	12
St. Thomas College, Scranton	M	2		5		2	1		11	9	12	21
St. Vincent's College, Latrobe	M	1	1			1			1	2	2	4
Schuylkill College, Reading				1						1		1
Shippensburg State Teachers College, Shippensburg		1								1		1
Slippery Rock State Normal, Slippery Rock		2								2		2
Swarthmore College, Swarthmore	A-M	5							6	5	6	11
Susquehanna University, Selinsgrove			1		2	1			4	1	7	8
Temple University, Philadelphia	M	4		4		21	2		8	29	10	39
Thiel College, Greenville	M	1						1	1	2	1	3
University of Pennsylvania, Philadelphia	A-M	17		16	2	31	20	5	49	69	71	140
University of Pittsburgh, Pittsburgh	A-M	7	1	57		18	7	3	23	85	31	116
Ursinus College, Collegeville	M			2	1	1	2		4	3	7	10
Villanova College, Villanova	M	8		9	2	16	2	1	11	34	15	49
Washington and Jefferson College, Washington	A-M	2		6	1		1	1	6	9	8	17
Waynesburg College, Waynesburg					1	2			1	2	2	4
Westminster College, New Wilmington	A-M				1				4		5	5
Wilson College, Chambersburg	A-M								1		1	1
RHODE ISLAND		3		11	1	2			19	16	20	36
Brown University, Providence	A-N	2		2	1				10	4	11	15
Providence College, Providence		1		9		2			7	12	7	19
Rhode Island State College, Kingston									2		2	2
SOUTH CAROLINA		9	2	9	2	12	4	1	23	31	31	62
Benedict Junior College,*† Columbia								1		1		1
Claflin Junior College,*† Orangeburg									1		1	1
Clemson College, Clemson	S	1		1		6			1	8	1	9
College of Charleston	S	1		1	1	2			1	4	2	6
Erskine College, Due West	S	1	1				1		3	1	5	6
Furman University, Greenville	S	1	1		1	2			3	3	5	8
Limestone College, Gaffney	S						2				2	2
Newberry College, Newberry									1		1	1
The Citadel, Charleston	S	1		1					5	2	5	7
University of South Carolina, Columbia	A-S	2		2		1			5	5	5	10
Wofford College, Spartanburg	S	2		4		1	1		3	7	4	11
SOUTH DAKOTA		8	1	10	5	3			4	21	10	31
Canton Lutheran Normal School, Canton		1								1		1
Columbus College, Sioux Falls				3		1			1	4	1	5
Dakota Wesleyan University, Mitchell	C	1		1						2		2
Huron College, Huron	C			1		1				2		2
Northern Normal and Industrial School, Aberdeen		1		1						2		2
Sioux Falls College, Sioux Falls		1								1		1
South Dakota Coll. of Agric. and Mechanic Arts, Brookings	C		1		2						3	3
South Dakota State School of Mines, Rapid City	C				1						1	1
Southern Normal School, Springfield				1						1		1
University of South Dakota, Vermillion	A-C	4		3	2	1			2	8	4	12
Yankton College, Yankton	C								1		1	1
TENNESSEE		45	6	44	6	41	3	4	33	135	54	189
Bethel College, McKenzie		2	1							2	1	3
Bryson College, Fayetteville		1				1				2		2
Carson Newman College, Jefferson City	S	1					1			1	1	2
David Lipscomb Junior College,* Nashville				1						1		1
East Tennessee State Teachers College, Johnson City	S			1				1	1	2	1	3
Fisk University,† Nashville		1	1	2		2		1	3	6	4	10
Freed Hardeman Junior College,* Henderson		1								1		1
George Peabody College for Teachers, Nashville	S	2		1						3		3
King College, Bristol				1						1		1
Knoxville College,† Knoxville		1							1	1	1	2
Lincoln Memorial University, Harrogate							1		[illegible]		[illegible]	[illegible]

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* Junior college. † Negro colleges.

Table A—*Sources of Premedical Education, First Year Students 1929-1930—Continued*

NAME OF COLLEGE	Accredited Agencies Approving	1 Year		2 Years		3 Years		4 Years		Totals		Grand Total
		No Degree	Degree	No Degree	Degree	No Degree	Degree	No Degree	Degree	No Degree	Degree	
TENNESSEE—Continued												
Lane College † Jackson									1		1	1
Maryville College Maryville	S	4				1			6	5	6	11
Middle Tennessee Teachers College Murfreesboro	S	1						1		2		2
Milligan College Milligan College				1						1		1
Nashville Agricultural Normal Institute * Madison		2		2						4		4
Roger Williams College † Nashville						1			2	1	2	3
Southern Junior College * Ooltewah		1								1		1
Southwestern Memphis	S	3	1	3		1			7	7	8	15
Tennessee Polytechnic Junior College * Cookeville		1		1						2		2
Tusculum College Greenville	S		1			1				1	1	2
Union College Jackson		2		7		1				10		10
University of Chattanooga	A-S			5	1	4			2	9	3	12
University of Tennessee Knoxville	A-S	12	1	14	1	8			2	34	4	38
University of Tennessee College of Pharmacy Knoxville				1						1		1
University of the South Sewanee	A-S			1			1		2	1	3	4
Vanderbilt University, Nashville	A-S	9	1	1	4	20		1	10	31	15	40
Walden University † Nashville		1								1		1
Ward Belmont * Nashville	S			1						1		1
West Tennessee State Teachers College Memphis	S	1		1		1				3		3
TEXAS		104	2	87	11	60	11	15	60	276	84	360
Abilene Christian College Abilene				1		1			2	2	2	4
Austin College Austin		4					2		2	4	4	8
A. and M College College Station	S	3		4	1	4		1	1	12	2	14
Baylor College for Women Belton	S	1							1	1	1	2
Baylor University Waco	S	10		22	5	2	2	1	6	35	13	48
Burleson Junior College * Greenville		1		3						4		4
Brownsville Junior College * Brownsville				1						1		1
College of Marshall * Marshall				1						1		1
Dallas University * Dallas		1		2						3		3
Daniel Baker College Brownwood				1						1		1
Decatur Baptist College * Decatur				3						3		3
Houston Junior College * Houston				1						1		1
Howard Payne College Brownwood						1			1	1	1	2
Hillsboro Junior College * Hillsboro		1								1		1
Jacksonville College * Jacksonville				1						1		1
John Tarleton Agricultural College * Stephenville	S	1		2						3		3
McMurray College, Abilene		1				2			1	3	1	4
Paris Junior College * Paris		1		1						2		2
Prairie View College † Prairie View						1				1		1
Rice Institute Houston	A-S	3		1		5		1	14	10	14	24
St. Edward's College Austin		1		1					2	2	2	4
St Mary's College San Antonio		2							1	2	1	3
Sam Houston College † Austin		3	1				1		3	3	5	8
Schreiner Institute * Kerrville		1		1						2		2
Simmons University Abilene	S	1		3		1				5		5
Southern Methodist University Dallas	A-S	8		6	2	8		3	2	25	4	29
South Park College * Beaumont		3		1						4		4
Southwestern University Georgetown	S	1		1		2	1		2	4	3	7
Southwest State Teachers College San Marcos	S	1		1		1			2	3	2	5
Stephen F Austin State Teachers College Nacogdoches	S	3								3		3
Texas Christian University Fort Worth	S	7			1	4	1	1	1	12	3	15
Temple Junior College * Temple		3								3		3
Texas Agricultural Junior College * Arlington		1		1						2		2
Texas School of Mines El Paso				2						2		2
Texas Technological College Lubbock	S	3		3		3			4	9	4	13
Thorpe Spring Christian College * Terrell		1								1		1
Trinity University Waxahachie	S			1					1	1	1	2
University of Texas Austin	A-S	29	1	25	2	25	4	8	10	87	17	104
University of Texas School of Pharmacy Galveston				1						1		1
Victoria Junior College * Victoria		1		1						2		2
Wayland Baptist Junior College * Plain View		1		2						3		3
Wesley Junior College * Greenville		1								1		1
West Texas State Teachers College Canyon	S	2								2		2
Wichita Falls Junior College * Wichita Falls		3		3						6		6
Wiley College † Marshall		1							4	1	4	5
UTAH		9		5	2	14	3	5	7	33	12	45
Agricultural College of Utah Logan	A-W	1			1	1	1		3	2	5	7
Brigham Young University * Provo	A-W	2				2			1	4	1	5
Dixie Junior College * St George				1						1		1
Latter Day Saints Junior College * Salt Lake City		1								1		1
Snow College * Ephraim		1								1		1
University of Utah Salt Lake City	A	4		4	1	11	2	5	3	24	6	30
VERMONT		4	1	16	25	1	5	6	3	27	34	61
Middlebury College Middlebury	A-N		1						2		3	3
Norwich University Northfield		1							1	1	1	2
St Michael's College Winooski Park		2								2		2
University of Vermont Burlington	A-N	1		16	25	1	5	6		24	30	54
VIRGINIA		23		53	5	54	13	12	84	142	72	214
Bridgewater College Bridgewater	S								2		2	2
College of William and Mary Williamsburg	A-S	4		12	2	7			5	23	7	30
Emory and Henry College Emory	S	2		1		1	2		5	4	7	11
Hampden and Sidney College Hampden Sidney	S				1						1	1
Hampton Normal and Industrial Institute † Hampton		1								1		1
Lynchburg College Lynchburg	S			1		2	1			3	1	4
Randolph Macon College Ashland	A-S	2		2		4			6	8	6	14
Randolph Macon Woman's College Lynchburg	A-S			1						1		1
Roanoke College Roanoke	S	1		2		1	2		2	4	4	8
University of Richmond	A-S	3		6		1		2	5	12	5	17
University of Virginia Charlottesville	A-S	7		14		37	2	8	8	66	10	76
Virginia Intermont College Bristol	S								1		1	1
Virginia Military Institute Lexington	S	1					1		10	1	11	12
Virginia Polytechnic Institute Blacksburg	S	1		8				2	1	11	1	12
Virginia Union University † Richmond					1				4		5	5
Virginia Theological Seminary and College † Lynchburg						1				1		1
Washington and Lee University Lexington	A-S	1		6			4		5	7	9	16
Medical College of Virginia School of Pharmacy Richmond					1		1				2	2

* Junior colleges　　† Negro colleges

Table A—*Sources of Premedical Education First Year Students 1929-1930—Continued*

Name of College	Accredited Agencies Approving	1 Year No Degree	1 Year Degree	2 Years No Degree	2 Years Degree	3 Years No Degree	3 Years Degree	4 Years No Degree	4 Years Degree	Totals No Degree	Totals Degree	Grand Total
WASHINGTON		**19**	**3**	**23**	**5**	**9**	**6**	**4**	**20**	**55**	**34**	**89**
College of Puget Sound Tacoma	W							1		1		1
Gonzaga University Spokane	W			3	2	1		1		5	2	7
St Martin's College Lacey		1								1		1
Seattle Pacific College* Seattle				1						1		1
State College of Washington Pullman	A-W	1		6		1	2		3	8	5	13
State Normal School Bellingham	W	3								3		3
State Normal School Seattle	A-W	1								1		1
University of Washington Cheney	A-W	5	1	5	3	6	3	2	16	18	23	41
Walla Walla College Walla Walla		7	1	8		1	1			16	2	18
Whitman College Walla Walla	A-W	1	1						1	1	2	3
WEST VIRGINIA		**23**	**3**	**31**	**4**	**5**	**3**	**1**	**17**	**60**	**27**	**87**
Bethany College Bethany	A-S C								1		1	1
Bluefield Colored Institute*† Bluefield		1				1				2		2
Broaddus College* Philippi									2		2	2
Concord State Normal School Athens		1		3						4		4
Davis and Elkins College Elkins		1								1		1
Fairmont State Normal Fairmont		2							2	2	2	4
Glenville State Normal Glenville				1						1		1
Marshall College Huntington	S-C	1		3		1	1		1	5	2	7
New River State School* Montgomery		2								2		2
Point Pleasant Normal School Point Pleasant		1								1		1
Potomac State School* Keyser	C	1								1		1
Salem College Salem				1						1		1
Shepherd College State Normal School Shepherdstown				1						1		1
West Liberty State Normal School West Liberty		1								1		1
West Virginia State College † Institute	C						1				1	1
West Virginia University, Morgantown	S	12	3	20	3	3	1	1	8	36	15	51
West Virginia Wesleyan University Buckhannon	C			2	1				3	2	4	6
WISCONSIN		**43**	**1**	**76**	**5**	**65**	**5**	**10**	**23**	**197**	**34**	**231**
Beloit College Beloit	A C			1			3		3	1	6	7
Campion College, Prairie du Chien		1								1		1
Carroll College Waukesha	C								3		3	3
Central State Teachers College Stevens Point		2		2						4		4
Eau Claire State Teachers College, Eau Claire		1								1		1
Lawrence College Appleton	A C	1		7					3	8	3	11
Marquette University Milwaukee	C	7		19	1	9		2	2	37	3	40
Milwaukee Downer College Milwaukee	A C	1								1		1
Milwaukee State Teachers College Milwaukee	C	9		4						13		13
Milton College Milton		1								1		1
Ripon College Ripon	A C	1				1	1		1	2	2	4
St Norbert's College De Pere					1						1	1
State Teachers College River Falls						1				1		1
State Teachers College Oshkosh	C			3						3		3
State Teachers College La Crosse		2		1								3
State Teachers College Superior		1		3					1	4	1	5
University of Wisconsin Madison	A C	19	1	36	3	54	1	8	10	117	15	132
WYOMING		**2**				**1**			**1**	**3**	**1**	**4**
University of Wyoming Laramie	A-C	2				1			1	3	1	4
U S POSSESSIONS		**4**	**1**	**10**		**9**			**3**	**23**	**4**	**27**
University of Hawaii Honolulu	A	2	1	7		5				14	4	18
University of the Philippines Manila		1								1		1
University of Porto Rico San Juan		1		3		4				8		8
CANADA		**4**		**1**		**3**			**3**	**8**	**3**	**11**
Acadia University Wolfville Nova Scotia						1			1	1	1	2
Loyola University Montreal Quebec				1						1		1
Manitoba Agricultural College Winnipeg Manitoba									1		1	1
McGill University Montreal Quebec	A	2				2				4		4
Stratford Collegiate University Stratford Ontario		1								1		1
University of Saskatchewan Saskatoon Saskatchewan									1		1	1
Victoria College Toronto Ontario	A	1								1		1
FOREIGN		**21**	**1**	**10**		**4**	**1**		**3**	**35**	**5**	**40**
American Institute LaPaz Bolivia S A				1						1		1
University of LaPaz, LaPaz, Bolivia, S A									1		1	1
Mackenzie College Sao Paulo Brazil S A		1								1		1
Fukien Christian University Soochow China		2								2		2
North China American School Peiping China				1						1		1
St Johns University Shanghai China		1								1		1
Shanghai Baptist College Shanghai China				1						1		1
Chosen Christian College Seoul Chosen						1				1		1
East London College London England			1								1	1
Howard Gardens Cardiff England		1								1		1
Middlesex Hospital School, London England		1								1		1
Royal Dental School London England						1				1		1
Stanborough College Watford England				1		1				2		2
Friedenau Seminar Friedenau Germany		1								1		1
Hamburg College-Institute Hamburg Germany		1								1		1
Neanderthal Seminary Neanderthal Germany		1		1						2		2
Oberrealschule, Bremen Germany				1						1		1
Oranienburg Normal School Oranienberg Germany		1								1		1
University of Berlin Berlin Germany		4								4		4
Royal Hungarian Univ of Budapest Budapest Hungary							1				1	1
Isabella Thoburn College Lucknow India				1						1		1
New Poona College Poona India		1								1		1
P Smith College Naini Tal India		1								1		1
Wellington College Bombay India		1								1		1
University of Rome Rome Italy		1								1		1
University of Guadalajara Guadalajara Mexico				1						1		1
Vilna University Vilna Poland		1								1		1
Enskilda Gymnasium Stockholm Sweden				1						1		1
Nyhyltan School Nyhyltan Sweden		1								1		1
American University Beyrouth Syria						1				1		1
University of St Joseph Beyrouth Syria		1								1		1
Roberts College Istanbul Turkey									2		2	2
University of Leningrad Leningrad U S S R				1						1		1

* Junior colleges † Negro colleges

(Continued from page 487)

Since 1924, a "College Blue Book" has been published under the direction of Hubert William Hurt, Ph D, of Columbia University This contains much valuable information about colleges, and gives by initials a list of the standardizing agencies (if any) by which each of 582 colleges has been approved

Lists of institutions commonly recognized as colleges of arts and sciences have been published in certain almanacs and year books, such as that published by the Chicago *Daily News* The list published in the yearbook just named includes the names of 523 institutions The present edition of the Council's "Approved Colleges of Arts and Sciences and Junior Colleges' includes the names of 549 institutions each of which is approved by one or more of the six different standardizing agencies which the Council deems worthy of being considered as reliable Beginning with the edition of April 20, 1920, the Council published the following statement in the introduction to its approved list

Table B—*Qualifications of Students Entering Medical Schools as Freshmen in Session of 1929-30*

	(a) From Colleges Approved by Accredited* Agencies	(b) Transferred to Approved Colleges After One or More Years Elsewhere	(c) From Other Colleges	(d) After One or More Years in an Approved College Transferred to Other Colleges	(e) Total Registration
University of Alabama School of Medicine	46	3	3		52
University of Arkansas School of Medicine	49	3	3	1	56
College of Medical Evangelists	32	13	76†	8	129
Stanford University School of Medicine	40	10		1	51
University of California Medical School	53	6		1	60
Univ of Southern California School of Med	40	5	1		46
University of Colorado School of Medicine	56	6	1		63
Yale University School of Medicine	41		1		42
Georgetown University School of Medicine	130	5	15	2	152
George Washington University Medical School	79	2	2	1	84
Howard University School of Medicine	45	4	9‡		58
Emory University School of Medicine	55	2			57
University of Georgia Medical Department	34	2	3		39
Loyola University School of Medicine	134	4	17	4	159
Northwestern University Medical School	113	9	3		125
University of Chicago Graduate School of Medicine of the Ogden Graduate School of Science and Rush Medical College	102	9	4	1	116
University of Illinois College of Medicine	170	3			173
Indiana University School of Medicine	100	11	8		119
State University of Iowa College of Medicine	130	15	7		152
University of Kansas School of Medicine	55	10	4	2	71
University of Louisville School of Medicine	71	5	6	1	83
Tulane University of Louisiana Sch of Med	129	2	1		132
Johns Hopkins University School of Medicine	67	2			69
University of Maryland School of Medicine and College of Physicians and Surgeons	160	4	5	2	171
Boston University School of Medicine	58	3	9		70
Harvard University Medical School	121	1	3		125
Tufts College Medical School	131	3			134
University of Michigan Medical School	142	7	11		160
Detroit College of Medicine and Surgery	72	4	11	5	92
University of Minnesota Medical School	157	9	6		172
University of Mississippi School of Medicine	35	3			38
University of Missouri School of Medicine	37	2	1		40
St Louis University School of Medicine	136	8	15	9	168
Washington University School of Medicine	75	4	3		82
Creighton University School of Medicine	76	10	3	7	96
University of Nebraska College of Medicine	65	7	23	5	100
Dartmouth Medical School	23				23
Albany Medical College	37	1	1		39
University of Buffalo School of Medicine	79	1			80
Columbia University College of Phys & Surg	113	1	1		115
Cornell University Medical College	60	1			61
Long Island College Hospital	118	1	1		120
New York Homeo Med Coll & Flower Hosp	92	3	3	4	102
University and Bellevue Hospital Med College	131	1	1	1	134
University of Rochester School of Medicine	38	1	1	2	42
Syracuse University College of Medicine	52				52
University of North Carolina School of Med	40	1			41
Wake Forest School of Medicine	28				28
University of North Dakota School of Med	28	2			30
University of Cincinnati College of Medicine	89		2		91
Western Reserve University School of Med	64	2	2		68
Ohio State University College of Medicine	98	2	1		101
University of Oklahoma School of Medicine	48	11	13	3	75
University of Oregon Medical School	60	3		1	64
Hahnemann Med College and Hosp of Phila	76	6	75§	13	170
Jefferson Medical College of Philadelphia	141	6	6	2	155
Temple University School of Medicine	106	3	1		110
University of Pennsylvania School of Medicine	108	2			110

Table B—*Qualifications of Students Entering Medical Schools as Freshmen in Session of 1929-1930—Continued*

•	(a) From Colleges Approved by Accredited Agencies	(b) Transferred to Approved Colleges After One or More Years Elsewhere	(c) From Other Colleges	(d) After One or More Years in an Approved College Transferred to Other Colleges	(e) Total Registration
Woman's Medical College of Pennsylvania	38	4	2		44
University of Pittsburgh School of Medicine	63	1	3		67
Medical College of the State of So Carolina	41		1		42
University of South Dakota School of Med	13	5	2	1	21
University of Tennessee College of Medicine	96	16	8	2	122
Meharry Medical College	23	4	35‡	4	66
Vanderbilt University School of Medicine	43	4	3		50
Baylor University College of Medicine	85	24	11	3	123
University of Texas School of Medicine	82	17	8		107
University of Utah School of Medicine	27	4			31
University of Vermont College of Medicine	51	2			53
Medical College of Virginia	70	7	5	2	84
University of Virginia Dept of Medicine	73				73
West Virginia University School of Medicine	53	7	7		67
University of Wisconsin Medical School	111	3	4		118
Marquette University School of Medicine	68	6	2		76
Totals	5,566	350	453	88	6,457
Per cent	86.2	5.4	7.0	1.4	100.0

* The agencies issuing lists of approved colleges of arts and sciences and junior colleges which have been considered reliable by the Council on Medical Education and Hospitals and which are referred to in these statistics as *accredited* consist of the five district Associations of Colleges and Secondary Schools and the Association of American Universities

† Heretofore the College of Medical Evangelists has been accepting students coming from colleges approved by the Association of Seventh Day Adventist Colleges and Secondary Schools some of which have not received the approval of the district Associations of Colleges and Secondary Schools

‡ Until in 1929 no satisfactory list of negro colleges had been prepared by a standardizing agency which could be considered as acceptable by the Council on Medical Education and Hospitals and the negro medical schools had no such list to guide them

§ The Hahnemann Medical College has admitted students coming from the Hahnemann School of Science which thus far has not obtained the approval of the district Association of Colleges and Secondary Schools

> After January 1, 1923, no college of liberal arts or sciences or junior college located in the district of the North Central Association of Colleges and Secondary Schools, which is *not* approved by that association, will be considered as acceptable by the Council on Medical Education

Later, as other of the district associations of colleges and secondary schools provided lists of approved colleges in their districts the foregoing ruling in regard to the 'North Central Association of Colleges and Secondary Schools" was changed and in the present edition (revised to June 1, 1930) reads

> No college of arts or sciences which is located in a district in which the Association of Colleges and Secondary Schools has established a commission for the approval of the colleges located in that district will be considered as acceptable to the Council on Medical Education and Hospitals unless it has been approved by the local district association of Colleges and Secondary Schools (see page 2) or by the Association of American Universities

STATISTICS ON PREMEDICAL EDUCATION

The accompanying statistics relate to the character of the premedical education of the students who entered on the study of medicine at the beginning of the present session—in the fall of 1929 These statistics are based on extensive reports, including the students individual histories, prepared by students and sent to us by the courtesy of the deans of the medical schools Through the receipt of such reports since 1910, the Council has been enabled to establish a Medical Students' Register at the headquarters of the Association This register has proved to be the source of much valuable information in regard to the preliminary histories and preparation of medical students

This year is particularly favorable for the presentation of the statistics, as the seventy-six recognized medical schools are not only requiring two or more years of college work for admission but seventy-five of them are rated in class A It is well, therefore, to take note regarding the character and standing of the educational institutions wherein the students entering medical schools last fall had obtained their premedical education

Table A gives a list, arranged alphabetically by states, of the liberal arts colleges, junior colleges and other institutions in which students obtained their premedical work This table shows, in the first column, whether or not the institution has been approved by one of the standardizing agencies which, after a careful consideration, have been deemed reliable by the Council on Medical Education and Hospitals In the succeeding columns the facts are indicated as to the number of students who obtained respectively one, two, three or four years of work in each of the colleges named and whether or not, following that work, each student was granted a degree The totals, also are given of students who obtained work in the institution named, including those who did not and those who did obtain degrees The last column gives the grand total of all students who obtained all, or a part, of their premedical work in each institution named

The table gives the totals for each state of the United States, and at the end of the list are given totals of students coming from the United States possessions, from Canada and from other foreign countries

Altogether, 8,402 students were reported as having attended 804 different colleges, an average of 10 4 students from each institution The statistics show that the qualifications of 6,457 students were obtained in these 804 colleges, which makes it evident that some students obtained credits from more than one college, and that each student, on the average, attended 1 23 colleges The numbers of students who attended one, two, three and four years at the colleges named were 1,864, 2,413, 1,846 and 2,279 respectively, or altogether 8,402 students, of whom 2,821 also obtained degrees Indeed, 2,821, or 43 7 per cent of all students entering medical schools in the fall of 1929, held baccalaureate degrees, as compared with 70 per cent of the 1930 graduates

Of the 804 colleges, junior colleges or other institutions in which these students obtained their premedical training, 452 have been approved by standardized agencies accredited by the Council and 352 have not been so approved Of the latter however, there are eleven who came from colleges in Canada, twenty-seven from colleges located in the United States dependencies, and forty are from colleges located in countries abroad Of these 33 colleges, an examination of the list reveals many which have well established reputations There are others, however, the standing of which, educationally, is not so well known

In the list also there are 125 junior colleges, only 41 of which have been approved by any of the accredited standardizing agencies The various district associations of colleges and secondary schools, therefore are urged to extend their investigations so as to cover junior colleges so that those which are found worthy may also be designated as "approved"

There are also thirty-one Negro colleges named in the list for which no satisfactory means of standardization had been found prior to 1929, when a list was prepared by a special committee acting under the auspices of the Council on Medical Education and Hospitals, pending the time when this work might be undertaken by the district associations of colleges and secondary schools Last year a list of seventy-eight Negro colleges was published, including twenty-five in group I (approved), fifteen in group II, thirty in group III and eight unclassified because of inadequate information

The students from Negro colleges who entered medical schools in the fall of 1929, therefore, obtained their premedical education before the Council's classification had been published This explains the conditions with which Meharry Medical College is contending

Three students are reported to have obtained their premedical training in schools of medicine, dentistry or pharmacy, and heretofore the educational value of that training would hardly be compared favorably with that obtained in approved colleges of arts and sciences The Council's ruling in regard to premedical work obtained in institutions the character of whose training is in doubt is as follows

> The premedical course in both quantity and quality should be such as could be accepted as the equivalent of the first two years of the course in reputable and approved colleges of arts and sciences leading to a baccalaureate degree

STUDENTS ADMITTED TO MEDICAL SCHOOLS

In table B, the first column (*a*) gives the number of students admitted to each medical school whose premedical training was obtained entirely in liberal arts colleges approved by either the Association of American Universities or one of the five district associations of colleges and secondary schools These are the agencies which the Council on Medical Education and Hospitals has believed to be sufficiently free from local, political or sectarian influences to be deemed worthy of the Council's endorsement

The second column (*b*) contains the number of students who began their premedical studies in colleges *not listed* as approved but who later transferred to, and finished their work in, colleges which *were approved* by reliable agencies All the work of these students, therefore, has supposedly been checked or scrutinized by the officials of colleges whose methods are known with greater certainty

The third column (*c*) shows the number of students who secured their work in liberal arts colleges or junior colleges which had not obtained the approval of the agencies accredited by the Council For some of these, through the courtesy of the deans, the Council has received statements setting forth the special reasons why the students were favorably considered Some of the students in the institutions referred to obtained credits in addition to the required minimum of sixty semester hours, and others obtained degrees from the colleges mentioned Still others however, obtained the bare minimum of sixty semester hours without any credits in advance even though the colleges attended had not been approved by any of the Council's accredited agencies In this group of students, however, forty obtained all their premedical work in foreign educational institutions, the exact status of which, educationally, may require careful investigation

The fourth column (*d*) indicates students who began their premedical study in approved colleges where they were under the supervision of instructors whose ability had thus been vouched for but who later migrated to colleges which were not so approved for the remainder of their premedical training It is assumed that the latter institutions are less apt to have scrutinized the students' previous work as thoroughly as would have been done by officers of more rigidly standardized colleges

Table B shows that 6,457 students were admitted to the first year classes of the seventy-four medical schools listed—an average of eighty-seven students per school Particularly pleasing is the fact that of these 6 457 students it is found that the premedical training of 5 916 or 91 6 per cent of all students was obtained in liberal arts colleges or junior colleges which have been investigated and approved by standardizing agencies considered as acceptable by the Council on Medical Education and Hospitals

Table C—*Sources of Premedical Work*

State	Number of Institutions	Totals by States										Grand Total
		1 Year		2 years		3 Years		4 Years		Totals		
		No Degree	Degree	No Degree	Degree	No Degree	Degree	No Degree	Degree	No Degree	Degree	
Alabama	9	21	5	25	6	16	6		27	62	44	106
Arizona	3	2	1	2	1	7	1		3	11	6	17
Arkansas	11	15	1	24	1	9		1	7	49	9	58
California	31	91	5	96	17	91	10	16	53	294	85	379
Colorado	7	28		15	1	17		3	10	63	11	74
Connecticut	5	6		6		10	7	2	48	24	55	79
Delaware.	1	1		1				1	7	3	7	10
Dist Columbia	6	65	9	82	7	20	5	8	35	175	56	231
Florida	4	6		10		6	1	2	10	30	11	41
Georgia	16	30	2	30	2	23	3		29	83	36	119
Idaho	5	6		2		1		1	2	10	2	12
Illinois	44	236	14	204	32	48	11	2	62	490	119	609
Indiana	23	49		73	6	27	9	6	56	155	71	226
Iowa	20	77	3	74	2	37	7	3	20	191	32	223
Kansas	24	35	1	27	3	22	6	2	29	86	39	125
Kentucky	18	32	5	33	4	23	12	1	17	89	38	127
Louisiana..	10	29		35	1	14	6		14	78	21	99
Maine	4	1		1	2	2	2	1	14	5	18	23
Maryland	12	12	1	15	5	12	25	1	43	40	74	114
Massachusetts	21	50	1	92	10	38	12		146	180	178	358
Michigan	27	61	8	64	19	88	15	10	93	223	135	358
Minnesota	18	45		76	5	75	3	6	21	202	29	231
Mississippi	11	13	2	28		7	3		11	48	16	64
Missouri	28	63	4	63	13	42	8	6	33	174	58	232
Montana	6	6		12	1	1	1		4	19	6	25
Nebraska	20	42	1	85	4	27	3	5	24	159	32	191
Nevada	1								2		2	2
New Hampshire	3	5		5	2	16	1	2	32	28	35	63
New Jersey	10	7	1	9		4	2	2	43	22	46	68
New Mexico	3	3		2					1	5	1	6
New York	40	143	3	167	17	220	38	14	417	544	475	1 019
North Carolina	20	17	2	14	4	24	6	1	58	56	70	126
North Dakota	5	6	1	10	1	14			6	30	8	38
Ohio	37	75	7	87	16	109	30	14	137	285	190	475
Oklahoma	16	29	1	39	1	17	6	1	15	86	23	109
Oregon	10	11		13	3	21	1	5	17	50	21	71
Pennsylvania	48	107	12	201	23	142	42	20	260	470	337	807
Rhode Island	3	3		11	1	2			19	16	20	36
South Carolina	11	9	2	9	2	12	4	1	23	31	31	62
South Dakota	11	8	1	10	5	3			4	21	10	31
Tennessee	30	46	6	44	6	41	3	4	39	135	54	189
Texas	45	104	2	97	11	60	11	15	60	276	84	360
Utah	6	9		5	2	14	3	5	7	33	12	45
Vermont	4	4	1	16	25	1	5	6	3	27	34	61
Virginia	18	23		53	5	54	13	12	54	142	72	214
Washington	10	19	3	23	5	9	6	4	20	55	34	89
West Virginia	17	23	3	31	4	5	3	1	17	60	27	87
Wisconsin	17	46	1	76	5	65	5	10	23	197	34	231
Wyoming	1	2				1			1	3	1	4
U S Possessions	3	4	1	10		9			3	23	4	27
Canada	7	4		1		3			3	8	3	11
Foreign	33	21	1	10		4	1		3	35	5	40
Totals	804	1 753	111	2 124	289	1,510	336	194	2 085	5 581	2,821	8 402

Of all students, 5 564 obtained all their premedical work in approved institutions while 350 others began their premedical work in colleges that were not approved but later transferred to and completed their work in colleges that were approved, all of their work, therefore, was investigated and vouched for by colleges that have been accredited by standardizing agencies

It is also remarkable that, of the seventy-four medical schools listed, only three were noted which accepted thirty or more students coming from colleges which have not been approved by the agencies recommended by the Council, and in all these, certain reasons are noted for the action taken, as shown by the footnotes

The overwhelming numbers of students who secured their premedical training in colleges approved by acceptable agencies illustrate the value of the list of approved colleges of arts and sciences and junior colleges as a means whereby prospective medical students may differentiate between colleges which are worthy of that title and those which are not so well organized including the smaller number which may be entirely unworthy As the list of approved schools becomes recognized, the unworthy type will have to improve or cease to exist

These statistics also give assurance that the students now entering medical schools have obtained a basic education in the fundamental sciences—physics, chemistry and biology—in colleges that have been considered as worthy A premedical training in approved colleges gives more assurance also that the students will have had a knowledge of English, whereby they can the better express their ideas in articles on subjects studied during their medical course, or in their subsequent practice as physicians

Table C shows the numbers of students taking their premedical work in each state, and those who have attended colleges in Canada or in other countries

PART II MEDICAL EDUCATION

The statistics presented for the year ended June 30, 1930, are based on reports received from the medical colleges and other reliable sources We acknowledge here the kind cooperation of the officers of the colleges who have made the compilation of these statistics possible

STATISTICS OF COLLEGES

Table 1, pages 500 and 501, gives the recognized medical colleges in session during 1929-1930, the population of the city, the rating given by the Council on Medical Education and Hospitals, the number of students, men and women, registered during the year, the number of 1930 graduates, men and women, the number of graduates holding collegiate degrees the number of teachers for each college, the number of weeks of actual instruction in the college year, the total fees for each year, the executive officer of the college, and the dates of beginning and ending of the next session The figures in heavy-faced type show the totals by states Beginning on page 525 are given the essential facts concerning all medical colleges arranged by states

All medical schools heretofore rated in class B have later secured the class A rating or have ceased to exist In 1927, Temple University College of Medicine at Philadelphia and Queen's University Faculty of Medicine Kingston Ontario were granted the class A rating, in 1928 Laval University Faculty of Medicine, Quebec, received the higher grade and in 1929 the same rating was given to the New York Homeopathic College and Flower Hospital In the light of scientific investigation, sectarianism in medicine has practically

(Continued on page 502)

TABLE 1—STATISTICS OF MEDICAL COLLEGES IN THE UNITED STATES, PHILIPPINE ISLANDS AND CANADA

Marginal No	NAME AND LOCATION OF COLLEGE	Population of City Where College Is Located (Census Bureau Estimate of 1930)	Classification by Council on Med Education	Number of Students Registered 1929-30: Men	Number of Students Registered 1929-30: Women	Graduates 1930: Men	Graduates 1930: Women	Graduates with A B, B.S. or Ph B	No of Teachers	Weeks in College Year	Total Fees (Dollars): 1st Year	Total Fees (Dollars): 2d Year	Total Fees (Dollars): 3d Year	Total Fees (Dollars): 4th Year	Executive Officer	Session of 1930 31: Begins 1930	Session of 1930 31: Ends 1931	Marginal No
	ALABAMA			102	1													
1	University of Alabama School of Medicine University (Tuscaloosa)*	20 010	A	102	1				20	30	221 50	241 50			Stuart Graves M D Dean	Sept 10	May 26	1
	ARKANSAS			160	2	29		20										
2	University of Arkansas School of Medicine Little Rock [3]	81 679	A	160	2	29		20	72	30	115	110	105	105	Frank Vinsonhaler M D Dean	Sept 15	June 2	2
	CALIFORNIA			809	82	148	12	136										
3	College of Medical Evangelists, Los Angeles [1][6]	1 231 730	A	311	27	63	5	44	213	38	258 50	218 50	334 50	316 50	Newton Evans M D Dean	July 2	June 21	3
4	Stanford University School of Medicine San Francisco [1]	625 074	A	178	15	40	2	42	207	43	387	311	315	315	William Ophüls M D Dean	Oct 1	June 15	4
5	University of California Medical School San Francisco [1][2]	625 074	A	105	32	45	5	50	182	35	[illegible]	[illegible]	225	225	Langley Porter M D Dean	Aug 19	May 17	5
6	University of Southern California School of Medicine Los Angeles	1 231 730	[9]	93	8				43	34	374	374			William D Cutter M D Dean	Sept 15	June 6	6
	COLORADO			193	12	38	5	25										
7	University of Colorado School of Medicine, Denver [3]	287 614	A	193	12	38	5	25	170	34	211	231	181	101	Maurice H Rees M D Dean	Sept 29	June 12	7
	CONNECTICUT			196	16	47	6	50										
8	Yale University School of Medicine New Haven	162 650	A	196	16	47	6	50	102	34	505	500	300	300	Milton C Winternitz, M D Dean	Sept 25	June 10	8
	DISTRICT OF COLUMBIA			1 018	17	205	4	96										
9	Georgetown University School of Medicine, Washington	485 716	A	515		100		20	187	34	370	360	360	375	John A Foote M D Dean	Sept 23	June 3	9
10	George Washington University Medical School Washington	485 716	A	270	9	44	1	21	172	36	422	422	422	388	William C Borden M D Dean	Sept 24	June 10	10
11	Howard University School of Medicine Washington	485 716	A	233	8	61	3	55	71	32	204 50	250 50	250 50	260 50	Numa P G Adams M D Dean	Oct 1	June 5	11
	GEORGIA			332	4	78	1	25										
12	Emory University School of Medicine Atlanta	317 001	A	193		49		20	133	32	270	255	255	280	Russell H Oppenheimer M D Dean	Sept 30	June 9	12
13	University of Georgia Medical Department, Augusta [3]	60 [illegible]	A	139	4	29	1	5	70	31	105	100	100	100	William H Goodrich M D Dean	Sept 27	June 8	13
	ILLINOIS			2 102	100	465	23	407										
14	Loyola University School of Medicine Chicago [1]	3 373 753	A	481	11	98	2	78	275	35	330	330	330	330	Louis D Moorhead M D Dean	Oct 1	June 11	14
15	Northwestern University Medical School Chicago [1]	3 373 753	A	508	14	121	4	78	351	33	355	355	355	355	Irving S Cutter M D Dean	Sept 26	June 15	15
16	University of Chicago Graduate School of Medicine of the Ogden Graduate School of Science	3 373 753	A	203	28				144	36	375	375	375	375	B C H Harvey M D Dean	Oct 1	June	16
17	University of Chicago Rush Medical College [1]	3 373 753	A	314	30	130	11	150	257	30			305	325	Ernest E Irons M D Dean	Oct 1	Aug 31	17
18	University of Illinois College of Medicine Chicago [1][2]	3 373 753	A	534	15	116	6	101	290	32	165	165	165	170	David John Davis M D Dean	Oct 6	June 6	18
	INDIANA			407	17	103		92										
19	Indiana University School of Medicine Bloomington Indianapolis [3]	364 073	A	407	17	103		92	233	34	175	175	175	175	Indianapolis—Charles P Emerson M D Dean Bloomington—B D Myers M D Dean	Sept 12	June 12	19
	IOWA			404	24	95	2	53										
20	State University of Iowa College of Medicine Iowa City [3]	10 500	A	404	24	95	2	53	94	34	192	192	192	192	Henry S Houghton M D Dean	Sept 22	June 1	20
	KANSAS			223	10	40	4	20										
21	University of Kansas School of Medicine Lawrence Kansas City [3][7]	392 040	A	223	10	40	4	20	138	35	162	154	155	160	Harry Roswell Wahl M D Dean	Sept. 18	June 8	21
	KENTUCKY			343	5	85	1	40										
22	University of Louisville School of Medicine Louisville	307 808	A	343	5	85	1	40	140	32	365	365	370	380	John Walker Moore M D Dean	Sept 15	May 29	22
	LOUISIANA			415	17	94	3	65										
23	Tulane University of Louisiana School of Medicine New Orleans	455 792	A	415	17	94	3	65	157	32	305	205	280	310	C C Bass M D Dean	Sept 24	June 9	23
	MARYLAND			654	43	141	15	110										
24	Johns Hopkins University School of Medicine Baltimore	801 741	A	250	33	57	12	69	360	34	610	610	610	610	Alan M Chesney M D Dean	Sept 30	June 9	24
25	Univ of Maryland School of Med and Coll of P & S Baltimore [3]	801 741	A	404	10	84	3	41	232	34	385	375	375	360	J M H Rowland M D Dean	Sept 29	June 6	25
	MASSACHUSETTS			1 181	41	285	4	192										
26	Boston University School of Medicine Boston [3]	783 161	A	205	20	43	4	32	148	32	300 50	300 50	303 50	400 50	Alexander S Begg M D Dean	Sept 21	June 17	26
27	Harvard University Medical School Boston	783 451	A	516		135		125	414	36	405	400	400	400	David L Edsall M D Dean	Sept 22	June 18	27
28	Tufts College Medical School Boston	783 451	A	460	21	107	10	35	240	32	357	352	352	352	A Warren Stearns M D Dean	Sept 24	May 29	28
	MICHIGAN			874	51	201	10	142										
29	University of Michigan Medical School Ann Arbor [3]	26,872	A	594	43	160	8	122	122	36	198	198	198	170 50	Arthur C Curtis M D Sec	Sept 29	June 22	29
30	Detroit College of Medicine and Surgery Detroit [1][2]	1 564 397	A	280	8	41	2	20	134	30	200	200	200	200	W H MacCraken M D Dean	Sept 25	June 20	30
	MINNESOTA			501	27	123	4	133										
31	University of Minnesota Medical School Minneapolis [1][2]	464 674	A	501	27	123	4	133	204	30	225	225	225	225	E P Lyon M D Dean	Sept 29	June 13	31
	MISSISSIPPI			64	2													
32	University of Mississippi School of Medicine University (Oxford)*[2]	2 710	10	64	2				17	34	163	163			10	Sept 17	June 2	32
	MISSOURI			902	10	193	4	111										
33	University of Missouri School of Medicine Columbia *[2]	10 700	A	74					32	35	141	146			Edgar Allen M D Dean	Sept 8	June 3	33
34	St Louis University School of Medicine, St Louis	822 032	A	530		[illegible]		61	206	32	380	345	345	335	Alphonse M Schwitalla Ph D Dean	Sept 23	June 1	34
35	Washington University School of Medicine St Louis	822 032	A	298	10	[illegible]	4	50	260	30	372	307	307	342	W McKim Marriott M D Dean	Sept 25	June 9	35
	NEBRASKA			548	8	108	3	90										
36	Creighton University School of Medicine Omaha	214 [illegible]	A	236	4	46	1	36	100	35	315	305	305	315	Hermann von W Schulte M D Dean	Sept 25	June 4	36
37	University of Nebraska College of Medicine Omaha [2]	214 [illegible]	A	312	4	62	2	54	171	35	217	212	212	212	C W M Poynter M D Dean	Sept 19	June 6	37
	NEW HAMPSHIRE			33														
38	Dartmouth Medical School Hanover	2,721	A	33					19	34	410	400			John P Bowler M D Dean	Sept 18	June 23	38

	NEW YORK			2 538	143	689	33	444										
39	Albany Medical College Albany	127 412	A	123	5	19	1	11	03	36	320	315	305	305	Thomas Ordway M D Dean	Sept 22	June 15	39
40	University of Buffalo School of Medicine Buffalo	572 913	A	275	9	65	3	51	213	34	527	527	517	525	Edward W Koch M D Dean	Sept 24	June 10	40
41	*Columbia University College of Phys and Surgs New York City*	6 938 792	A	390	33	97	7	101	603	33	555	520	570	540	William Darrach M D Dean	Sept 24	June 3	41
42	Cornell University Medical College New York City Ithaca	6 938 402	A	205	30	47	9	56	233	34	510	500	560	515	G Canby Robinson, M D Director	Sept 29	June 11	42
43	Long Island College Hospital New York City-Brooklyn	2 308 500	A	431	7	100		49	158	32	545	560	530	560	Adam M Miller A M Dean	Sept 29	June 8	43
44	New York Homeopathic Medical College and Flower Hospital	6 938 792	A	315	9	70	3	46	150	34	510	500	500	550	Claude A Burrett M D Dean	Sept 15	June 2	44
45	University and Bellevue Hospital Medical College New York City	6 938 702	A	471	24	110	4	120	204	35	535	523	512	533	Samuel A *Brown M D Dean*	Sept 17	June 10	45
46	University of Rochester School of Medicine Rochester	325 010	A	191	12	21	3	20	118	34	400	400	400	400	George H Whipple M D Dean	Sept 22	June 15	46
47	Syracuse University College of Medicine Syracuse	209 267	A	177	8	42	3	20	150	34	400	400	400	410	Herman G Weiskotten M D Dean	Sept 10	June 1	47
	NORTH CAROLINA			131	4													
48	University of North Carolina School of Medicine Chapel Hill *	2 607	A	68	4				12	35	220	220			I H Manning M D Dean	Sept 10	June 4	48
49	Duke University School of Medicine Durham *	47 600	A						100		150	150	150	150	Wilburt C Davison M D Dean	Oct 1	June 13	49
50	Wake Forest College School of Medicine Wake Forest	1 527	A	63				10	16	30	270	225			Thurman D Kitchin M D Dean	Sept 16	June 4	50
	NORTH DAKOTA			63														
51	University of N Dakota School of Med University (Grand Forks)* ²	15 400	A	63					13	35	65	65			H E French M D Dean	Sept 16	June 9	51
	OHIO			786	49	160	13	132										
52	*University of Cincinnati College of Medicine* ¹ ²	440 331	A	356	17	51	4	43	174	35	360	360	300	320	Arthur C Bachmeyer M D Dean	Sept 22	June	52
53	Western Reserve University School of Medicine Cleveland	901 432	A	222	10	50	4	53	206	34	380	385	385	385	Torald Sollmann M D, Dean	Sept 18	June 18	53
54	Ohio State University College of Medicine Columbus ²	290 560	A	208	13	59	5	36	122	34	186	186	186	191	John H J Upham, M D Dean	Sept 3	June 9	54
	OKLAHOMA			217	5	46	1	46										
55	University of Oklahoma School of Medicine, Oklahoma City *	182 845	A	217	5	46	1	46	109	36	128	105.50	23	23	LeRoy Long M D Dean	Sept 15	June 2	55
	OREGON			213	14	41	1	42										
56	University of Oregon Medical School Portland ²	200 122	A	213	14	41	1	42	211	33	200	195	100	100	Richard B Dillehunt M D Dean	Oct 3	June 11	56
	PENNSYLVANIA			2 052	148	462	22	315										
57	Hahnemann Medical College and Hospital of Philadelphia	1 961 428	A	470		78		27	138	31	355	362	362	375	William A Pearson M D Dean	Sept 20	June 11	57
58	Jefferson Medical College of Philadelphia	1 961 428	A	580		140		60	294	34	410	410	425	425	Ross V Patterson M D Dean	Sept 22	June 5	58
59	Temple University School of Medicine Philadelphia	1 961 428	A	285	5	53		11	172	35	415	390	390	390	William N Parkinson M D Dean	Sept 24	June 18	59
60	University of Pennsylvania School of Medicine Philadelphia	1 961 428	A	485	13	125	4	120	391	33	520	500	500	500	William Pepper M D Dean	Sept 26	June 17	60
61	Woman's Medical College of Pennsylvania Philadelphia	1 961 428	A		110		14	7	78	36	350	375	400	400	Martha Tracy M D Dean	Sept 24	June 10	61
62	University of Pittsburgh School of Medicine Pittsburgh	669 817	A	216	14	56	4	51	204	34	415	400	400	410	Raleigh R Huggins M D, Dean	Sept 22	June 10	62
	SOUTH CAROLINA			165	4	33	2	20										
63	Medical College of the State of South Carolina, Charleston	62 123	A	165	4	33	2	20	75	35	185	185	100	100	Robert Wilson M D Dean	Sept 25	June 4	63
	SOUTH DAKOTA			48														
64	*University of South Dakota School of Medicine Vermillion* *	2,850	A	48					11	35	50	50			George R. Albertson M D, Dean	Sept 17	June 6	64
	TENNESSEE			786	22	187	5	114										
65	University of Tennessee College of Medicine Memphis	252 049	A	333	9	81	2	35	107	44	133.50	113.50	108.50	118.50	Orren W Hyman Ph D Admin Offic	July 11	June 10	65
66	Meharry Medical College Nashville	153 153	A	202	4	38		31	53	32	218	210	210	220	John J Mullowney M D Pres	Oct 1	May 28	66
67	Vanderbilt University School of Medicine Nashville	153 153	A	187	9	45	3	48	152	35	315	315	315	320	Waller S Leathers M D Dean	Sept 23	June 10	67
	TEXAS			657	22	120	5	67										
68	Baylor University College of Medicine Dallas	260,397	A	361	10	103	3	36	125	33	312	297	287	287	Walter H Moursund M D Dean	Sept 20	June 1	68
69	*University of Texas School of Medicine Galveston* ²	51 630	A	296	12	17	2	31	58	31	62	78	60	60	*George E Bethel M D Dean*	Oct 1	May 30	69
	UTAH			60	1													
70	University of Utah School of Medicine Salt Lake City *	140 058	A	60	1				21	30	101	151			B I Burns, M D Dean	Sept 29	June 6	70
	VERMONT			146	10	27	3	17										
71	University of Vermont College of Medicine Burlington ²	24 789	A	146	10	27	3	17	55	36	327.50	327.50	300	300	James N Jenne M D Dean	Sept 10	June 15	71
	VIRGINIA			508	15	146	4	76										
72	Medical College of Virginia Richmond ²	182 883	A	300	6	91	2	40	138	35	300	307.50	292.50	322.50	Manfred Call M D Dean	Sept 16	June 2	72
73	University of Virginia Dept of Med University (Charlottesville)²	15 151	A	208	9	55	2	27	60	36	200	200	205	255	J Carroll Flippin M D Dean	Sept 18	June 16	73
	WEST VIRGINIA			107	3													
74	West Virginia University School of Medicine Morgantown * ²	14 100	A	107	3				10	35	115	115			John N Simpson M D Dean	Sept 11	June 9	74
	WISCONSIN			543	26	80	4	60										
75	University of Wisconsin Medical School Madison ² ⁴	57 815	A	342	22	28	2	18	110	36	155	133	101	120	Charles R Bardeen M D Dean	Sept 21	June 22	75
76	Marquette University School of Medicine Milwaukee ¹	578 249	A	201	4	52	2	42	101	34	361	351	354	350	Bernard I McGrath M D Dean	Sept 20	June 10	76
	PHILIPPINE ISLANDS			1 194	62	89	3	5										
77	University of the Philippines College of Med and Surg Manila ¹¹	285 306	A	298	62	28	3	5	102	37	101.75	91.25	61.25	60.25	Fernando Calderon M D Dean	June 10	Mar 21	77
78	University of St Thomas Faculty of Medicine and Surgery Manila ¹¹	285 306	A	896		61			51	36	92.05	92.05	92.05	92.05	Jose Luis de Castro M D, Dean	June 18	Mar 15	78
	CANADA ⁵			2 860	134	425	23	177										
79	University of Alberta Faculty of Medicine Edmonton Alta	60 744	A	155	14	18	2	10	78	30	150	220	270	220	Allen C Rankin M D Dean	Sept 29	May 15	79
80	Dalhousie University Faculty of Medicine Halifax N S	60 000	A	161	1	19		10	61	31	225	225	225	225	John Stewart M D Dean	Sept 9	May 12	80
81	Queen's University Faculty of Medicine Kingston Ont	21 653	A	296		40		10	51	30	171	170	179	201	Frederick Etherington M D Dean	Sept 24	May 27	81
82	University of Toronto Faculty of Medicine Toronto Ont	569 910	A	660	68	99	11	29	202	30	171	220	200	230	*Alexander Primrose M D Dean*	Sept 30	May 23	82
83	University of Western Ontario Medical School London Ont.	60 950	A	133	15	29	1	7	41	31	200	200	208	233	A B Macallum M D Dean	Sept 24	May 20	83
84	McGill University Faculty of Medicine Montreal Que	1 012 185	A	412	17	91	1	20	101	35	207	207	207	207	C F Martin M D Dean	Sept 17	May 20	84
85	University of Montreal Medical Faculty Montreal, Que	1 012 185	A	276	1	41	1	30	105	36	225	207	211.80	210 0	Louis de Lotbinière Harwood M D Dean	Sept 20	June 15	85
86	Laval University Faculty of Medicine Quebec Que	130 000	A	251		45		30	61	35	160	170	160	160	Arthur Rousseau M D Dean	Sept 9	June	86
87	University of Manitoba Faculty of Medicine Winnipeg, Man	209 347	A	210	18	44	3	4	130	32	205	200	210	210	S Willis Prowse M D Dean	Sept 29	May 6	87

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* *Gives only the first two years of the medical course*

# The figures given are 1930 estimates furnished by the Bureau of the Census

1 Hospital internships required for graduation See table 4 for the fifth year registration

2 The following universities make an additional charge for nonresidents Arkansas $100 California $300 Colorado $150 Georgia $300 Illinois $50 *Indiana $75 Iowa* $[illegible] *Kansas* $50 Maryland $150 Michigan $80 Detroit $50 Minnesota $75; Mississippi $50 Missouri $10 per term Nebraska varies according to states of residence North Dakota, $15 Ohio State, $105 Cincinnati $50 (nonresidents of Cincinnati) Oklahoma, $200 Oregon $60 South Dakota $50 Texas $150 Vermont $75 Virginia $50 Medical College of Virginia $100 West Virginia $250 and Wisconsin $150

3 Total fees are $5 additional *each year for men*

4 Wisconsin's fourth year session is forty eight weeks

5 See College Items for fifth and sixth year fees

6 Twelve months each for first two years See College Items

7 The population given is for Kansas City Kansas and Kansas City Missouri

8 The figures are for 1930 1931

9 At the business meeting of the Council on Medical Education and Hospitals held in Detroit June 23 24 1930 the Council voted that an acceptable status be granted for the students of this school who had *finished the two years of work during the sessions 1928-29 and 1929 30* The granting of an acceptable rating for the medical school however was further postponed pending developments apparently in process

10 The rating of this institution is in doubt because of reports relating to sweeping changes recently ordered in the faculties of both the University of Mississippi and its medical school

11 The figures given are for the 1928 29 session

Dr. Robert [illegible] Libr
[illegible] Medical College
2986

(Continued from page 499)

disappeared Two schools remain which still bear homeopathic titles, but they are teaching pharmacology and therapeutics in the same manner as other acceptable schools

HOME STATES OF MEDICAL STUDENTS

Table 2, pages 502 and 503 shows from what states the students came who were in attendance at each medical college during the session of 1929-1930 The states having medical colleges naturally contribute larger numbers of students than those which have no medical colleges [2]

The state furnishing the largest number of students this year was New York with 3,103, followed by Pennsylvania with 1,931, Illinois with 1,366, and Ohio with 1,265 There were 1,445 students who came from the twelve states not having medical schools four of these states furnished more than 100 students each, these being New Jersey, 755, Washington, 130, Rhode

TABLE 2—*Distribution of Medical*

Marginal Number	NAME OF COLLEGE	1 251 Alabama	2 27 Arizona	3 183 Arkansas	4 707 California	5 170 Colorado	6 219 Connecticut	7 53 Delaware	8 131 Dist Columbia	9 118 Florida	10 292 Georgia	11 46 Idaho	12 1,366 Illinois	13 674 Indiana	14 589 Iowa	15 303 Kansas	16 300 Kentucky	17 202 Louisiana	18 90 Maine	19 290 Maryland	20 703 Massachusetts	Marginal Number
1	University of Alabama School of Medicine	49	1	1				1			5		1			2	4					1
2	University of Arkansas School of Medicine	2		111	1	1				1			1	4	1			1				2
3	College of Medical Evangelists			2	71	5	3		6	2		4	8	7	7	16	3		2	4	8	3
4	Stanford University School of Medicine		2	1	160	2						2		2	1	1						4
5	University of California Medical School				210																	5
6	University of Southern California School of Medicine		1		91										1					1		6
7	University of Colorado School of Medicine	2			15	133	1						4	1	1	2					1	7
8	Yale University School of Medicine				3		75			1	1		1	1	3				5		18	8
9	Georgetown University School of Medicine				1		25	1	64			1		1					1	11	30	9
10	George Washington University Medical School	2	3		6		5	1	72			3		1			1			8	1	10
11	Howard University School of Medicine	11		5			1		21	5	13		1			2	1	4		9	3	11
12	Emory University School of Medicine	3					1			16	107			1								12
13	University of Georgia Medical Department	1									154						1					13
14	Loyola University School of Medicine				4	4	2			6			257	9	7		1				3	14
15	Northwestern University Medical School	2	3		30	4						9	205	17	13	15	2	1			1	15
16	University of Chicago Graduate School of Medicine of *the Ogden Graduate School of Science*	2	2			1	1	1			1	2	190	9	11	7	3				8	16
17	University of Chicago Rush Medical School	8	2	3	2	1	2			4	1	4	94	14	25	5	3	1			1	17
18	University of Illinois College of Medicine	2			1								490	3	4	2	1				2	18
19	Indiana University School of Medicine												2	407			1					19
20	State University of Iowa College of Medicine	1										1	5		448	2					1	20
21	University of Kansas School of Medicine				2	2							1		1	177						21
22	University of Louisville School of Medicine	7		1	1		1			2		1	5	22	1	1	177					22
23	Tulane University of Louisiana School of Medicine	55		9	5	1	1		1	27	6		1				2	16				23
24	Johns Hopkins University School of Medicine	9		4	15	1	14	2	3	2	5	1	5			1	2		7	37	11	24
25	*University of Maryland Sch of Med & Coll of P & S*				1		10	3	3				1				1			151	2	25
26	Boston University School of Medicine				1		13									2			15		100	26
27	Harvard University Medical School	6	1		16	5	10	1	2	3	7	3	14	5	5	10	5	1	15	4	134	27
28	*Tufts College Medical School*						45												12		340	28
29	University of Michigan Medical School	2	2		5	1	3		2	3	2	2	6	14	1		6		1		9	29
30	Detroit College of Medicine and Surgery		1											2								30
31	University of Minnesota Medical School	1			5	1	1		1				6	1	3	1						31
32	University of Mississippi School of Medicine				1																	32
33	University of Missouri School of Medicine												2				1					33
34	St Louis University School of Medicine	1	4	1	14	3	5			3		3	37	8	2	10	1	2			5	34
35	Washington University School of Medicine			7	10	3				1		2	38	6	2	14	[illegible]				1	35
36	Creighton University School of Medicine				42		1				1	2	7		31	13	1					36
37	University of Nebraska College of Medicine					3							2		3	6						37
38	Dartmouth Medical School				1	3	2		1						1						8	38
39	Albany Medical College																		1		6	39
40	University of Buffalo School of Medicine				2																2	40
41	Columbia University College of Physicians and Surgeons	1			3	1	17	1	1	1	3	1	2		1		1		1	2	9	41
42	Cornell University Medical College	2	1		8		4		1		2			2	1	1			4	2	7	42
43	Long Island College Hospital				1	1	12						1						2		1	43
44	New York Homeopathic Med Coll & Flower Hospital						3			1			1	3								44
45	University and Bellevue Hospital Medical College				1		11							1					1	1	2	45
46	University of Rochester School of Medicine				1		7				1		1						2	4	7	46
47	Syracuse University College of Medicine						1						1									47
48	University of North Carolina School of Medicine										1						1					48
49	Wake Forest College School of Medicine																	1				49
50	University of North Dakota School of Medicine																					50
51	University of Cincinnati College of Medicine				3				1				1	8		1	18			1		51
52	Western Reserve University School of Medicine			1						3			1	3	1	1	1			1		52
53	Ohio State University College of Medicine																					53
54	University of Oklahoma School of Medicine	3																				54
55	University of Oregon Medical School					4						2										55
56	Hahnemann Medical Coll and Hospital of Philadelphia				1		2	6					2	2	1	1	3		2		7	56
57	Jefferson Medical College of Philadelphia	1	1		3		14	5	1	9			2	2	1		1		2	6	8	57
58	Temple University School of Medicine	1					1			2			1	1	1		1			1	1	58
59	University of Pennsylvania School of Medicine	4			5		3	6	1	11		1	5	2	1	2	7		4	2	5	59
60	Woman's Medical College of Pennsylvania	1		1	2		1	3					1	2	1	1	1			4	3	60
61	University of Pittsburgh School of Medicine																					61
62	Medical College of the State of South Carolina	1							1		1											62
63	University of South Dakota School of Medicine														6		1					63
64	University of Tennessee College of Medicine	21		16	2					4			2			1	11	8				64
65	Meharry Medical College	9		7	2			1	4	7	8		13	2	1		2	8		3	3	65
66	Vanderbilt University School of Medicine	13		8	1					3	2	1	1	3		2	23					66
67	Baylor University College of Medicine	1	2	4	1					1				1	2		2	9				67
68	University of Texas School of Medicine																					68
69	University of Utah School of Medicine											2										69
70	University of Vermont College of Medicine				1		11												1		16	70
71	Medical College of Virginia	1	1				1		2	1	1		1				2		1	3		71
72	University of Virginia Department of Medicine	4		1				1	5	2			1				2	1		4	1	72
73	West Virginia University School of Medicine				1																	73
74	University of Wisconsin Medical School	1										1	12	3						1		74
75	Marquette University School of Medicine						2						6	2	2	1			1		1	75
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	

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[2] Compare with table A in the State Board Number of The Journal, April 26 1930 p 1308

Island, 127, and Florida 118 Of these noncollege states, New Mexico had twenty-three, Nevada twelve and Wyoming twelve There were 155 students who came from government possessions, Hawaii, Porto Rico and the Philippine Islands, and 155 from foreign countries

NUMBER OF STUDENTS BY CLASSES

In table 3, page 504, the students enrolled in each college are shown by classes The total attendance for the first year was 6,457, or 180 more than last year, for the second year 5,496, or 961 more than last year, for the third year 4,931, or 185 more than last year, while in the fourth year there were 4,713, or 162 more than in 1929

FIFTH YEAR MEDICAL STUDENTS

There are now eleven medical schools which require that students shall have completed a fifth year as an intern in an approved hospital before they are eligible

Students by States

Marginal Number	21 Michigan 330	22 Minnesota 610	23 Mississippi 104	24 Missouri 488	25 Montana 78	26 Nebraska 382	27 Nevada 12	28 New Hampshire 53	29 New Jersey 788	30 New Mexico 23	31 New York 3 103	32 North Carolina 433	33 North Dakota 129	34 Ohio [illegible]	35 Oklahoma 470	36 Oregon 60	37 Pennsylvania 1 631	38 Rhode Island 127	39 South Carolina 230	40 South Dakota 111	41 Tennessee 334	42 Texas 830	43 Utah 144	44 Vermont 111	45 Virginia [illegible]	46 Washington 130	47 West Virginia 233	48 Wisconsin 603	49 Wyoming 14	50 U S Possessions Philippines etc 155	51 Foreign 231	Totals 21 597	Marginal Number
1			1						8		22	2		2	1		2				1	2			1		1				3	103	1
2			4	7					1	1	3			1	7		2			1	1	4					3			1		162	2
3	18	14		1	2	7	1		2	3	12	2	4	5	8	13	5	1		4	7	6				10		5	1	11	62	[illegible]	3
4		1			2		1						1			4	2					1	12			2				3	3	183	4
5						1			1		4																			1	1	227	5
6							1			1				1									1			1				2		101	6
7	2		1	4	1				2	1	6		1			2				1		2	5			2		4	1	2	4	205	7
8	3	1		2	2	1		3	16	3	43	2		3		1	7	4				2		1	2		1			4	3	212	8
9	1	1			1			3	60		120			12			113	20	1					2	10	1	2			1	12	616	9
10	1	1		1					22	1	70	1	1	10		1	23	1	1			2	4		13	2	2	1		11	2	279	10
11	1		5	3		1			14		6	15		7	1		17		16	1	3	6			20						50	241	11
12	1		10						1		5	5		1	1		2		5		3	1			3		2	2			4	190	12
13									1																1	1				1		140	13
14	26	6		2	1	1			11	1	67		1	34	1	1	20	1		1						3		20		0	10	496	14
15	30	11	1	7	7	7			4	1	2	3	18	12	4	1	2			7		6	30			21	2	41	1	5	2	522	15
16	24	1		5	1	3		1	5	1	12	2	2	11	3	3	5	1		4		9				1		10	1	0	9	291	16
17	20	8		15	3	4			4		13	4	9	12	1	1	15			11	3	9	[illegible]	1	1	2	9	19		4	6	344	17
18	2	1	6	1	8						2		3							5	1		3			2	1	11		1	2	540	18
19									1		7			8			2													1		424	19
20		3		2		1	1		11		22	1			1					3						1				2	2	508	20
21				34							1			1	1	1				1		1						2		5	3	233	21
22	2	1	6	8	1				5	2	21	5	1	32	1	1	6	1			4	3	5		1	3	12	3		3	3	348	22
23	1	1	43	4					1		15	10		1	5				1	1	6	45			2		1			2	11	472	23
24	8	3	2	2	1			1	12	1	34	13	1	8			10	3	5	2	3	8	1	2	13	2	7	4			6	263	24
25								4	43		88	21		4			[illegible]						1		2	1	24			6	2	414	25
26	1					1		12	10		28	1		2			[illegible]	17			1			2	1	1				2	4	210	26
27	12	8	1	11	4	4	1	4	[illegible]	1	61	12	1	24		7	21	11		6	3	11	6	4	3	11	6	16	1	1	8	516	27
28	1				1			9	10		31			2			6	15						2						10		487	28
29	390	3		4	5	1			10		35	2	2	73	1	4	21					2				4	2	5	1	2	7	[illegible]	29
30	269													11			2										1					280	30
31		445		1	12	3					4		12	1						9		1				2		14	1	2	1	628	31
32		50									3			1							1	1										60	32
33				65					1	1	1							1				1									1	74	33
34	7	11		121	[illegible]	2	1		25		67	1	3	93	1	6	31	5		2	4	8	1			6	1	5		8	1	530	34
35		2		142	1	1			5		11	6	2	7	1	3	4		1	4	4	0	3		1	3		0		7	1	308	35
36		6		4	7	65	1				15		4	2	1	4	2			[illegible]		2	2			7		1	2	3		240	36
37	1	4		3		300							5							7		1	2			1		2	7	4		316	37
38				1	1			8	4		6			2		1	4							1								39	38
39											118						1															128	39
40		1							3		238			6			10														2	281	40
41	3	1	4	1				2	65		261	2	1	1			10	2	3		2	1	2	2	2			1		6	6	423	41
42		1		1			1	1	22		168	1		4			9	3						1		2					1	241	42
43									97		[illegible]	1		1			8	2							1		7			6	1	438	43
44									18		316			7			4														1	354	44
45	1								61		350	3	1	2		1	9	2								1	7					495	45
46	1				1		1		3		[illegible]			14			11						1			1	1				4	173	46
47									10		139	3					2	2												3	4	185	47
48											3	71					1		1		1				1							82	48
49									1			48							1						2							53	49
50	1	3			2						1		54															1		1		63	50
51	3										2	2		238													3	2				285	51
52						1	2				4			103			17				1					1	4	1	1	1	3	241	52
53														310													1					311	53
54				1											217		1															222	54
55					3										204											12				2		227	55
56	5	1		1		1			73		32			10		1	202	10				1				1				1	5	470	56
57	2	1	2	5	2	2		2	42		16	29	1	51		1	151	9	6		4	3	2		2	3	7	1		5	3	[illegible]	57
58	1							1	22		10	2		7			233	2	1						1							290	58
59	1	1	3	6		1		1	34		19	41	1	16			[illegible]		2		6	0	11		11	6	2	6		1	4	478	59
60	1			1		1		2	8		23	2		3		1	35	1	1	1	2	1	1		2		1	2		2	1	110	60
61											1			1			251													1		260	61
62												2		1					15									1				[illegible]	62
63		3		1		2					1			1			2			24		1				1		1		1	1	46	63
64			41	7					1		8	8		7	10				2		244	12			1	1	1				1	405	64
65	5		11	6				1	7		13	10		8	1		7		12		3	21			6		7	1			5	206	65
66	3		17	2					1		5	12		3	2		5	1	5	1	61	5			4			1			1	196	66
67			2	1						5			1		6	1					1	329									2	371	67
68				1			1															303										303	68
69																1	1						[illegible]						1		2	61	69
70								3	8		20							2						[illegible]							1	[illegible]	70
71			1						5		6	60		2			1		2		2	1			[illegible]	1	41			1	2	[illegible]	71
72			4						8		9	4	1				2		4		6	1			[illegible]		6				1	[illegible]	72
73											4			10			12										7			6		110	73
74	2	4				1					7		1	2		1	2			1			1					207			1	201	74
75	0	4		1	2	1			2		5		2	8			3	1								1		[illegible]		1	2	[illegible]	75
	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51		

to receive the M D degree These schools and the number of students enrolled in their fifth year are given in table 4

Of the eleven colleges, a total of 1,081 students are enrolled in the fifth year

As a matter of fact, it is estimated that about 90 per cent of all students obtain this internship whether required to do so or not, so that the number of students who will be serving their internships during the next year will amount to slightly more than 4 000 Of the students taking internships, also, about three fourths will be obtaining their internships voluntarily This shows how valuable the intern year is, in the opinion of recent graduates Other data regarding the instruction of interns appear on page 508

Table 3—*Medical Students Shown by Classes*

Name of College	Enrolled During 1929 30 1st	2d	3d	4th	
University of Alabama School of Medicine	62	51			103
University of Arkansas School of Medicine	56	43	33	30	162
College of Medical Evangelists	129	76	87	78	370
Stanford University School of Medicine	51	50	43	49	193
University of California Medical School	60	53	54	60	227
University of So California School of Med	55	46			101
University of Colorado School of Medicine	63	48	51	43	205
Yale University School of Medicine	42	61	54	55	212
Georgetown University School of Medicine	152	155	101	107	515
George Washington University Med School	84	73	71	51	279
Howard University School of Medicine	58	57	58	68	241
Emory University School of Medicine	57	45	48	40	190
University of Georgia Medical Department	30	42	29	39	140
Loyola University School of Medicine	159	127	116	94	496
Northwestern University Medical School	125	127	133	137	522
University of Chicago Grad School of Med of the Ogden Graduate School of Science	116	137	35	3	291
University of Chicago Rush Medical College			141	203	344
University of Illinois College of Medicine	173	128	128	120	549
Indiana University School of Medicine	119	94	106	105	424
State University of Iowa College of Medicine	152	147	102	107	508
University of Kansas School of Medicine	71	59	54	49	233
University of Louisville School of Medicine	83	88	89	88	348
Tulane Univ of Louisiana School of Med	132	97	103	100	432
Johns Hopkins University School of Med	69	72	72	70	283
Univ of Md Sch of Med and Coll of P & S	131	99	96	88	414
Boston University School of Medicine	70	54	48	47	219
Harvard University Medical School	125	123	131	137	516
Tufts College Medical School	134	112	122	119	487
University of Michigan Medical School	160	143	170	166	639
Detroit College of Medicine and Surgery	62	71	71	62	266
University of Minnesota Medical School	172	143	113	100	528
University of Mississippi School of Medicine	38	28			66
University of Missouri School of Medicine	40	34			74
St Louis University School of Medicine	168	122	115	125	530
Washington University School of Medicine	82	71	78	77	308
Creighton University School of Medicine	96	43	52	49	240
University of Nebraska College of Medicine	100	84	67	65	316
Dartmouth Medical School	23	16			39
Albany Medical College	39	38	30	21	128
University of Buffalo School of Medicine	80	66	70	68	284
Columbia Univ College of Phys and Surgs	115	102	102	104	423
Cornell University Medical College	61	56	68	56	241
Long Island College Hospital	120	109	109	100	438
New York Homeopathic Medical College and Flower Hospital	102	88	81	83	354
University and Bellevue Hospital Med Coll	134	110	128	123	495
University of Rochester School of Medicine	42	33	34	24	133
Syracuse University College of Medicine	52	53	35	45	185
University of North Carolina School of Med	41	41			82
Wake Forest College School of Medicine	26	27			53
University of North Dakota School of Med	30	33			63
University of Cincinnati College of Medicin	91	73	61	58	283
Western Reserve University School of Med	68	58	60	55	241
Ohio State University College of Medicine	101	70	79	61	311
University of Oklahoma School of Medicine	75	56	44	47	222
University of Oregon Medical School	64	58	60	45	227
Hahnemann Med Coll and Hosp of Phila	170	131	101	78	480
Jefferson Medical College of Philadelphia	155	148	143	140	586
Temple University School of Medicine	110	61	65	54	290
University of Pennsylvania School of Med	110	104	134	130	478
Woman s Medical College of Pennsylvania	44	33	24	15	116
University of Pittsburgh School of Medicine	67	67	66	60	260
Medical Coll of the State of South Carolina	42	39	41	37	159
University of South Dakota School of Med	21	25			46
University of Tennessee College of Medicine	122	98	98	87	405
Meharry Medical College	66	51	49	40	206
Vanderbilt University School of Medicine	50	48	50	48	196
Baylor University College of Medicine	123	88	73	87	371
University of Texas School of Medicine	107	83	75	43	308
University of Utah School of Medicine	31	30			61
University of Vermont College of Medicine	53	42	31	30	156
Medical College of Virginia	84	88	97	97	366
University of Virginia Dept of Medicine	73	64	49	59	245
West Virginia University School of Medicine	67	43			110
University of Wisconsin Medical School	118	99	48	39	304
Marquette University School of Medicine	75	64	65	61	265
Totals for 1930	6,457	5 496	4 931	4 713	21,597
Totals for 1929	6 277	5,304	4 746	4,551	20,878
Totals for 1928	6,199	5 190	4 646	4,510	20 545

Table—4—*1929-1930 Fifth Year Students in Medical Colleges Requiring the Hospital Intern Year for the M D Degree*

College of Medical Evangelists	69
Stanford University School of Medicine	48
University of California Medical School	40
Loyola University School of Medicine	90
Northwestern University Medical School	126
University of Chicago Rush Medical College	236
University of Illinois College of Medicine	125
Detroit College of Medicine and Surgery	43
University of Minnesota Medical School	184
University of Cincinnati College of Medicine	65
Marquette University School of Medicine	55
Total	1 081

Table 5—*Medical Colleges Students and Graduates*

Year	No Colleges	Students	Graduates	A.B or B.S	Per Cent
1880	100	11,826	3,241		
1890	133	15 404	4 454		
1900	160	25 171	5 214		
1904	160	28 142	5 747		
1906	162	25 204	5,364		
1910	131	21 526	4 440	680	15.3
1915	96	14,891	3,536	858	24 3
1920	85	13 798	3 047	1 331	43.5
1921	83	14 466	3 192	1 465	46 0
1922	81	16 140	2 529	1 455	57.5
1923	80	16 960	3 120	1 787	57.3
1924	79	17 728	3,562	2,050	66 7
1925	80	18 200	3 974	2 431	61.2
1926	79	18 840	3 962	2 388	60.3
1927	80	19 662	4 035	2,480	61.5
1928	80	20 545	4 262	2 708	63.5
1929	76	20 878	4 446	2 951	66 4
1930	76	21 597	4 565	3 211	70 0

Table 6—*Women in Medicine*

Year	Women Students	Percentage of All Students	Women Graduates	Percentage of All Graduates
1904	1,129	4.0	198	3 4
1910	907	4 5	116	2 6
1915	592	4.0	92	2 6
1920	818	6.0	122	4 0
1925	910	5 0	204	5 1
1926	935	5 0	212	5 4
1927	964	4 9	189	4 7
1928	929	4 5	207	4 9
1929	925	4 4	214	4 8
1930	955	4 4	204	4 5

NUMBER OF COLLEGES

The number of medical colleges in each decade since 1850 and in certain special years is shown in table 5 The largest number was in 1906, when there were 162 medical schools Largely through the merging of two or more schools into one, in each of a score or more of cities, the number has gradually decreased until in 1924 only seventy-nine medical schools remained With the opening of the new medical school of the University of Rochester, N Y, in 1925, the number was restored to eighty

INSTITUTIONS NO LONGER RECOGNIZED AS MEDICAL SCHOOLS

The charters of two class C institutions were revoked, respectively, June 23, 1926, and May 23, 1927, after they had been convicted of being engaged in the sale of medical diplomas

Kansas City College of Medicine and Surgery
St. Louis College of Physicians and Surgeons

Two other institutions were promptly chartered, evidently as successors for the two just closed, they were conducted in the same buildings and by the same faculties, evidently, as their predecessors and therefore were no more worthy of recognition

American Medical University
Missouri College of Medicine and Science

Four other institutions, from official reports, for several years had been refused recognition by the licensing boards of forty-six states and the territory of Alaska These are

Chicago Medical School
College of Physicians and Surgeons, Boston
Middlesex College of Medicine and Surgery, Cambridge, Mass
Kansas City University of Physicians and Surgeons

In 1928, therefore, the Council on Medical Education and Hospitals decided to retain them no longer among recognized medical schools Their omission reduced the number of recognized medical schools to seventy-four Last year the Eclectic Medical College of Cincinnati was suspended, leaving seventy-three colleges, but two other medical schools were opened, one at the University of Chicago, the other at the University of Southern California, and this fall the new Medical School of Duke University will be opened This gives a list of seventy-five recognized medical schools

TABLE 7—*Medical Colleges Students and Graduates by States*

State	Colleges	Students Men	Students Women	Graduates Men	Graduates Women	Graduates with A B or B S
Alabama	1	102	1			
Arkansas	1	169	2	29		20
California	4	809	82	148	12	136
Colorado	1	103	12	38	5	25
Connecticut	1	106	16	47	6	50
District of Columbia	3	1 018	17	205	4	96
Georgia	2	332	4	75	1	25
Illinois	5	2,102	100	465	23	407
Indiana	1	407	17	103		92
Iowa	1	484	24	95	2	53
Kansas	1	223	10	40	4	20
Kentucky	1	343	5	85	1	40
Louisiana	1	415	17	94	3	65
Maryland	2	654	43	141	15	110
Massachusetts	3	1 181	41	285	14	192
Michigan	2	874	51	201	10	142
Minnesota	1	501	27	129	4	183
Mississippi	1	64	2			
Missouri	3	902	10	106	4	111
Nebraska	2	548	8	108	3	90
New Hampshire	1	30				
New York	9	2,598	143	580	23	444
North Carolina	3	131	4			
North Dakota	1	63				
Ohio	3	786	49	100	13	132
Oklahoma	1	217	5	46	1	46
Oregon	1	213	14	41	1	42
Pennsylvania	6	2,052	148	452	22	357
South Carolina	1	155	4	33	2	20
South Dakota	1	46				
Tennessee	3	785	22	167	5	114
Texas	2	657	22	126	5	67
Utah	1	60	1			
Vermont	1	146	10	27	3	17
Virginia	2	596	15	148	4	76
West Virginia	1	107	3			
Wisconsin	2	543	26	88	4	80
Totals	76	20 642	955	4 361	204	3,211
		21 597		4 565		

The organization of the medical school of the University of Southern California is still incomplete, so that this school is not ready to receive an acceptable rating

An upheaval at the University of Mississippi has resulted in an uncertainty in regard to the future standing of its medical school

NUMBER OF MEDICAL STUDENTS

The total number of medical students in the United States (table 5) for the year ended June 30, 1930, excluding premedical, special and postgraduate students, was 21,597, an increase of 719 over last year This is the largest enrolment of students since 1909, or twenty years ago, when 22,145 students were enrolled in the 140 medical schools then existing Since 1919 there has been an average increase in enrolment of 433 students each year

NUMBER OF MEDICAL GRADUATES

The total number of graduates for the year ended June 30, 1930, was 4,565, or 119 more than last year

Although the total number of graduates decreased from 5,747 in 1904 to 2,529 in 1922, the number of graduates coming from class A medical schools has increased from 267 in 1906 to 2,929 in 1921 The lower number graduating in 1922 is due to the World War and represents the students who began as freshmen in 1918 All medical schools are now in class A, so that all the 4,565 are of class A grade Note that since 1922 the number of graduates has rapidly increased until this year 4,565 graduated

WOMEN IN MEDICINE

Table 7 shows that during the last year there were 955 women studying medicine, or thirty-two more than last year The percentage of women to all medical students this year is 4 42 There were 204 women graduates this year, ten less than last year The percentage of women to all medical graduates was 4 47 These percentages, indeed, have fluctuated only slightly since the tabulation of these facts was begun in 1904 The lowest percentage of women was 3 2, both of students and graduates in 1912, and the highest was 6 1 in 1922 when the 'war class' was graduated

MEDICAL GRADUATES AND BACCALAUREATE DEGREES

Of the 4 565 medical graduates (table 7) 3,211, or 260 more than last year had also obtained degrees in arts and sciences This year 70 per cent of all graduates held collegiate degrees, as compared with only 15 3 per cent of the graduates in 1910 As noted in table 8, of the 3,211 graduates holding baccalaureate degrees, 444, the largest number, came from the New York medical colleges The Illinois schools reported 407, Pennsylvania, 357, Massachusetts, 192, California, 136, and Ohio, 132 All of the medical schools are now requiring two or more years of college work for admission, which brings more students within reach of the combined courses for the B S and M D degrees

The best premedical preparation is believed to be that obtained by students in the courses leading to the degree of Bachelor of Arts or Science in the college or university attended, since on the university campus they come in contact with students preparing for various other professions or line of activity and have obtained a knowledge of such professions and activities before selecting their own life work

It must not be inferred from these statements that a baccalaureate degree should in any sense be made a requirement for the obtaining of either a medical degree or the right to practice medicine With the requirement of two or more years of premedical study, medical education in the United States is now on a par with the requirements in other countries There is no objection to any medical school which so desires to require entrance qualifications in excess of two years, and students who have the time and means also are urged to continue their college education and obtain the degree It is believed, however, that provision should always be made for students otherwise exceptionally qualified who would be put to much inconvenience to obtain the two extra years of college work

From the first, the Council on Medical Education and Hospitals has believed that for medical licensure the maximum premedical requirement legally should not exceed two years of college education

COLLEGES, STUDENTS AND GRADUATES BY STATES

As shown in table 8, New York now has nine medical colleges—the largest number—followed by Pennsylvania with six and Illinois with five.

TABLE 8.—*College Fees 1930-1931*

	Colleges	Per Cent		Colleges	Per Cent
$ 50 to 99	3	3.9	$300 to 349	10	13.1
100 to 149	6	7.9	350 to 399	15	19.8
150 to 199	12	15.9	400 to 499	8	10.5
200 to 249	9	11.8	500 to 599	7	9.2
250 to 299	5	6.6	600 to 699	1	1.3
Totals				76	100.0
Average fee per student				$300	

New York has the largest number of students enrolled in its medical schools, 2,681, followed by Illinois with 2,202, Pennsylvania with 2,200, and Massachusetts with 1,222. New York leads also in the number of graduates, having reported 622, followed by Illinois with 488, Pennsylvania with 474 and Massachusetts with 299.

TABLE 9.—*Increase in Medical College Fees During Sixteen Years*

	Showing for each Year the Number and Percentage of Colleges Requiring																		
	$50 or Less		$50 to $100		$100 to $150		$150 to $200		$200 to $250		$250 to $300		$300 to $350		$350 to $450		$450 to $650		Total Colleges
Year	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%	
1910	7	5.3	39	29.3	62	46.6	22	16.5	2	1.5	1	0.8							133
1911	2	1.7	33	27.5	54	45.0	27	22.5	4	3.3									120
1912	2	1.7	17	14.7	61	52.5	32	27.6	3	2.6	1	0.9							116
1913	3	2.8	20	18.9	43	40.6	34	32.1	5	4.7	1	0.9							106
1914	5	4.9	11	10.8	44	43.1	35	34.3	6	5.9	1	1.0							102
1915	6	6.4	10	10.6	31	33.0	38	40.5	7	7.4	2	2.1							94
1916	6	6.5	13	14.0	23	24.7	41	44.1	8	8.6	2	2.1							93
1917	5	5.3	11	11.6	29	30.5	39	41.0	7	7.4	4	4.2							95
1918	5	5.6	11	12.4	22	24.7	35	39.3	12	13.5	4	4.5							89
1919	5	5.8	9	10.6	14	16.5	35	41.2	18	21.2	4	4.7							85
1920	3	3.5	9	10.5	19	22.3	27	32.0	19	22.3	4	4.7	3	3.5	1	1.2			85
1921	3	3.6	7	8.4	15	18.2	25	30.1	18	21.7	7	8.4	7	8.4	1	1.2			83
1922	3	3.7	7	8.6	13	16.1	19	23.5	19	23.5	9	11.1	10	12.3	1	1.2			81
1923	2	2.5	7	8.7	6	7.5	22	27.5	18	22.5	11	13.8	13	16.3	1	1.2			80
1924	1	1.3	5	6.3	8	10.1	21	26.6	14	17.7	14	17.7	13	16.5	3	3.8			79
1925			6	7.5	6	7.5	20	25.0	13	16.3	13	16.2	19	23.7	3	3.8			80
1926			4	5.1	7	8.9	14	17.7	13	16.4	14	17.7	18	22.8	6	7.6	3	3.8	79
1927			5	6.4	5	6.4	17	21.8	11	14.0	15	19.3	15	19.3	5	6.4	5	6.4	78
1928			3	4.1	5	6.7	12	15.8	11	14.5	8	10.6	15	19.2	17	22.4	5	6.7	76
1929			3	4.0	5	6.6	12	16.0	9	12.0	7	9.4	13	17.3	19	25.4	7	9.4	75
1930			3	3.9	6	7.9	12	15.9	9	11.8	6	7.9	10	13.2	21	27.6	9	11.8	76

TUITION AND OTHER FEES

In table 1, pages 500 and 501, are given the amounts charged by the various medical colleges per annum for tuition, matriculation, and laboratory and graduation fees for each student. In table 9, the seventy-six colleges have been grouped according to the amount of fees charged. Ten colleges charge fees of less than $150 a year, twenty-one charge from $150 to $250, fourteen from $250 to $350, fifteen charge from $350 to $400, eight colleges charge between $400 and $500, seven charge between $500 and $600, and one charges more than $600. The average fee per student in all colleges is $307. The nine colleges charging less than $150 are all schools of medicine of state universities, the fees referred to being for residents of those states. It is customary for state university medical schools to charge higher fees for students coming from other states. These charges are shown in a footnote to table 1.

MEDICAL SCHOOL FEES DURING NINETEEN YEARS

Tuition fees in medical schools have been gradually increased during the last nineteen years. From 1910 to 1915, the majority of medical schools were charging fees of $150 or less. From 1916 to 1922 the majority were charging fees above $150, while since 1920 the majority have included several medical schools charging more than $300. The percentage of medical schools charging more than $300 increased from 4.7 in 1920 to 52 per cent in 1929. Now, forty-six (61.3 per cent of all colleges) are charging fees over $250 per student, and seven (9.3 per cent) are charging over $500. The average fees charged per student by all colleges in 1910 was $118, in 1915 it had increased to $145, in 1920, to $180, in 1925, to $250, in 1930 to $307.

In 1910, several medical schools were still paying all expenses—and a few were making profits—from students' fees. At present, however, no medical college can maintain the extensive laboratories, pay the essential instructors and properly teach modern medicine without having an income much larger than that received alone from students' fees.

As the cost of conducting medical schools has increased, there has also been an increase—and properly so—in the fees charged for tuition. A large provision has been made for scholarships and loan funds for the benefit of deserving students who may be lacking financially. With such financial aid such students will be enabled to use their entire time in obtaining a larger experience in examining more patients while under teachers who are also skilled clinicians.

Chart 1 shows the *decline* in the number of medical colleges *from 1904 to 1929* inclusive and the *increase* in the numbers of those which adopted, respectively, one and two or more years of college work for admission. Thus it will be seen that the decrease was in the numbers of the lower standard colleges. As noted in the present statistics, there are now seventy-six medical schools all but one of which is rated in class A.

Chart 2 shows the relative number of physicians in proportion to population for forty-one countries. Note that the United States has 1,266 physicians for each 100,000 of the population, thereby having a far more generous supply than any other country. Austria comes next, followed by Great Britain.

Note also the countries at the other extreme in their order they are Persia, Siam, Bolivia, Guatemala, etc.

The figures are based on direct correspondence with the countries named or information from other sources considered reliable.

With the constantly increasing numbers of students and graduates, there is no need of any alarm regarding the supply of physicians in the United States the next quarter century,

LIFE CHART OF MEDICAL COLLEGES

Attention is called to the chart appearing on pages 510 to 513 which shows by a series of vertical dark bands the years during which each of 315 medical colleges in the United States were in existence. Viewing the page as one opens the book, each of the light horizontal lines represents a year as mentioned at the right and left markings. The sixteen colleges organized prior to 1825 are mentioned in the inset appearing on page 512.

At the bottom of each page opposite to its vertical dark band is given the key number and name of each college the date it was organized and, if extinct, the year it was closed.

A break in any dark band connected with a dotted line indicates the years during which the institution was suspended. Such suspensions as will be noted in the chart were common among the medical schools of the South during the Civil War (1861-1865). Shaded lines indicate that (*a*) only the first two years of the medical course were offered, (*b*) medical degrees were granted by the university as an examining body although no actual medical teaching was done, (*c*) no degrees were granted (*d*) only a preparatory course was given (*e*) only the last two or clinical years were given (*f*) degrees bearing the name of the university were granted for work done in another medical school which also granted degrees, and (*g*) the college was reported as not in good standing with its own state medical licensing board. Colleges are grouped to bring together those which have been merged. The bands representing colleges merged are connected by pen lines.

FEWER BUT BETTER MEDICAL SCHOOLS IN THE UNITED STATES

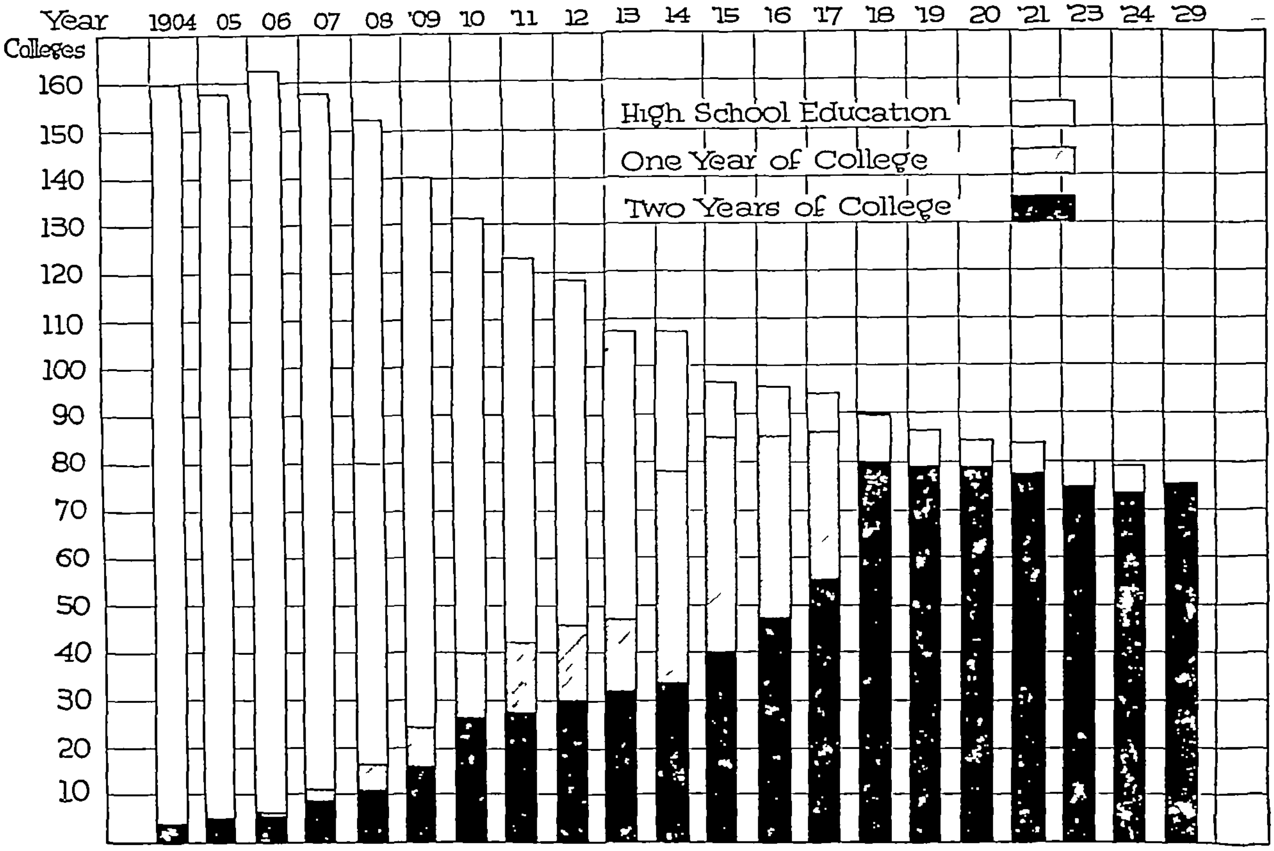


Chart 1.—Showing the increasing requirements of premedical education

SPECIAL INSTANCES OF MEDICAL SCHOOL MERGERS

Particular attention is called in the chart to the groups of colleges merged in Indiana, Kansas and Kentucky.

In Indiana, prior to 1905, three medical schools were giving the full four year course and at Indiana University was given a preparatory course for students intending to study medicine. Overtures were made by Indiana University whereby the three medical schools would merge and be taken over by the university. The three medical schools were merged, but instead of joining with Indiana University they united with Purdue University, a school of technology. Thereupon a medical school was opened at Indiana University offering the first two years in medicine. In 1906 a medical school was organized at Indianapolis offering the work of the last two years in medicine and in 1907 this clinical school was united with Indiana University School of Medicine. Thereby the state of Indiana had two medical schools one of which was connected with the state university and the other connected with a school of technology both of which offered four year courses in medicine and both of which were expecting to receive from the state funds for their maintenance. Because of this rivalry it appears that considerable feeling was developed. A year later, however, in 1908, a meeting was called to which was invited prominent medical educators in various parts of the country. As a consequence the two schools were united as the Indiana University School of Medicine.

In Kansas City, since 1900, six medical schools including five in Missouri and one in Kansas, were merged into what is now the University of Kansas School of Medicine

In Kentucky, five medical schools underwent a merger whereby two were merged into the University of Louisville and two became the Louisville and Hospital Medical College, but for certain reasons the Kentucky School of Medicine was omitted in the merger In 1908, however, by common consent all of the medical schools merged into what is now the University of Louisville School of Medicine

PHYSICIANS IN THE UNITED STATES AND ABROAD

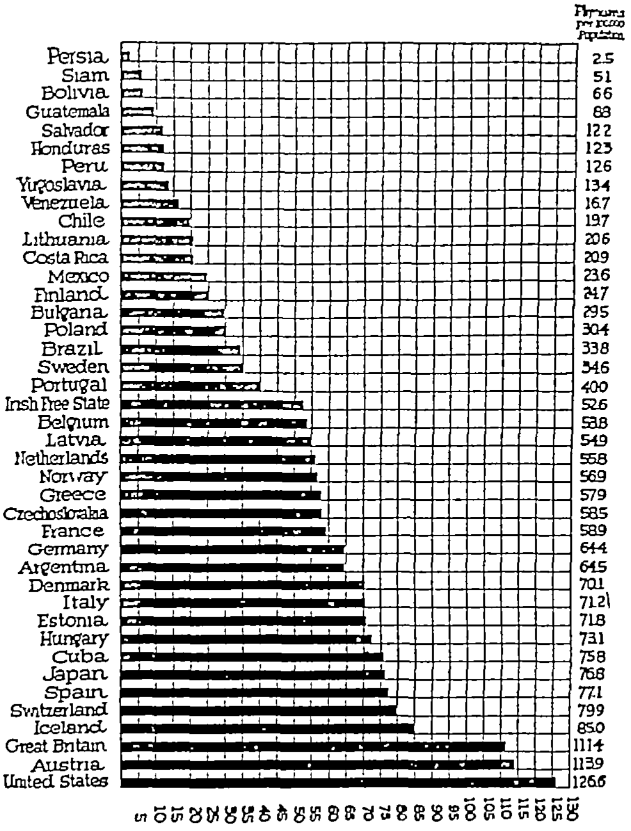


Chart 2 —Supply of physicians to population

In Tennessee, between 1909 and 1912, four medical schools, two previously located at Nashville and two in Memphis, were merged into what has since been known as the University of Tennessee School of Medicine

This chart brings up to date the Life Chart of Medical Colleges which was published in The Journal, Aug 28, 1913, on pages 578 to 581 inclusive, and since that time the number of schools has been reduced from 107 to 76

A number of medical schools which enrolled no students and others which were reported as fraudulent or otherwise not in good standing—altogether about 150 institutions—have been omitted from the chart

An investigation of the chart will show that a large proportion of the medical schools which ceased to exist in the last fifty years have done so through merging with other medical schools Most of these medical schools which merged had been rated in classes A or B Of those which became extinct, however, a large proportion had been rated in class C by the Council on Medical Education and Hospitals

Part III Hospital Intern Service

A SUMMARY OF REPORTS FROM 1 491 PHYSICIANS REGARDING THEIR INTERN EXPERIENCE

In accordance with a custom established several years ago, the Council on Medical Education and Hospitals again addressed an inquiry to former interns regarding the type of service provided in hospitals using interns This survey was general in nature, not being restricted to those 648 institutions at present on the Council's list of hospitals approved for intern training

A total of 1,491 reports were received, representing 700 hospitals, of which 493 are approved for intern training In some instances four and five reports were received on the same institution This survey has enabled the Council to summarize in a systematic manner the facilities of the individual hospitals for rendering a valuable fifth year in medicine, to note the intern's participation in surgery and obstetrics, to secure further data on the rotating service as compared with the straight service, to estimate the extent to which clinical-pathologic conferences and staff meetings are utilized in the instruction of the interns, to gage the amount of laboratory and x-ray work assigned to them as well as to gather other valuable information pertinent to the intern hospital

Table 1 —*Instruction and Supervision of Interns*

State	Number of Reports from Ex Interns	No Hospitals Represented	Approved for Internships	Interns Attended Staff Conferences			Attended Clinical Meetings and Lectures			Interns Report Staff Supervision		
				Yes	No	Indefinite	Yes	No	Indefinite	Yes	No	Indefinite
Alabama	12	6	2	10	2		4	7	1	6	5	1
Arizona												
Arkansas	4	3	1	3	1			4		4		
California	62	30	25	53	8	1	46	14	2	48	13	1
Colorado	17	7	6	17			9	8		13	4	
Connecticut	29	11	11	27	2		20	8	1	27	2	
Delaware	5	2	1	5			3	2		5		
Dist Columbia	18	9	6	17	1		11	7		14	4	
Florida	8	4	3	6	1	1	2	5	1	5	3	
Georgia	19	12	6	16	2	1	13	5	1	17	2	
Idaho	1	1		1				1			1	
Illinois	125	68	30	110	10	5	79	43	3	109	16	
Indiana	37	12	11	36		1	24	12	1	33	4	
Iowa	20	6	6	20			11	9		16	3	1
Kansas	12	5	4	12			5	7		9	3	
Kentucky	17	10	6	14	1	2	7	7	3	13	4	
Louisiana	15	11	6	15			7	6	2	14		1
Maine	7	4	4	7			3	3	1	6		1
Maryland	32	15	13	27	4	1	19	13		31	1	
Massachusetts	71	32	23	67	3	1	43	25	3	64	6	1
Michigan	52	23	18	50		2	34	15	3	42	10	
Minnesota	32	14	13	29	3		24	6	2	26	6	
Mississippi	1	1			1			1			1	
Missouri	53	24	10	53			40	11	2	51	1	1
Montana												
Nebraska	10	7	5	9		1	7	2	1	9	1	
Nevada												
New Hampshire	1	1	1	1			1			1		
New Jersey	75	30	25	71	1	3	40	29	6	61	13	1
New Mexico												
New York	247	128	74	223	21	3	139	101	7	220	27	5
North Carolina	9	6	3	5	4		3	6		5	3	1
North Dakota	1	1	1	1			1			1		
Ohio	78	36	24	71	4	3	48	26	4	70	7	1
Oklahoma	5	2	2	5			2	3		5		
Oregon	13	5	5	13			8	5		11	1	1
Pennsylvania	174	89	66	163	7	4	110	61	3	159	12	3
Rhode Island	12	6	2	12			7	3	2	11	1	
South Carolina	11	7	2	11			4	7		8	1	2
South Dakota												
Tennessee	20	11	9	18	2		11	8	1	20		
Texas	40	18	1[illegible]	39		1	17	18	5	36	4	
Utah	14	5	5	13	1		8	6		9	5	
Vermont	7	3	1	7			3	3	1	7		
Virginia	36	18	6	32	3	1	19	16	1	32	4	
Washington	29	10	9	29			11	14	2	19	10	
West Virginia	11	5	3	9	2		2	9		9	2	
Wisconsin	49	20	18	49			34	13	2	42	7	
Wyoming												
Totals	1 491	700	492	1,370	81	31	881	549	61	1 288	182	21

Of the 43 states represented in the data received, the rgest number of reports for any one state refer to ew York hospitals These reports, 247 in number, over 74 approved intern hospitals and 54 hospitals not pproved for intern training, 174 reports were received n Pennsylvania hospitals, and 125 on hospitals of Illinois No reports were received on hospitals in Arizona, Montana, Nevada, New Mexico, South Dakota and Wyoming

TABLE 2—*Surgical Training*

State	1st Assistant	2d Assistant	3d or 4th Assistant	Unanswered	Minor Surgery Yes	Minor Surgery No	Minor Surgery Unanswered	Major Surgery Yes	Major Surgery No	Major Surgery Unanswered	No Surgical Department	Total Reports
Alabama	12				12			8	4			12
Arizona												
Arkansas	4				4			3	1			4
California	41	20	1		53	9		28	34			62
Colorado	11	3	1		12	3		6	9		2	17
Connecticut	25	2		2	26		3	24	3	2		29
Delaware	4	1			5			4	1			5
Dist Columbia	15	3			18			12	6			18
Florida	7	1			7	1		6	2			8
Georgia	14	3	1	1	18	1		10	9			19
Idaho	1				1			1				1
Illinois	108	14	1	1	120	4		73	51		1	125
Indiana	28	9			36		1	17	20			37
Iowa	14	5		1	17	3		11	8	1		20
Kansas	11	1			9	3		5	7			12
Kentucky	10	6	1		17			8	9			17
Louisiana	9	6			14	1		9	6			15
Maine	6			1	7			7				7
Maryland	21	6			25	2		6	19	2	5	32
Massachusetts	60	6	1	1	64	3	1	50	17	1	3	71
Michigan	36	10	6		40	8	4	17	32	3		52
Minnesota	21	11			29	3		19	13			32
Mississippi	1				1			1				1
Missouri	35	8	6	1	48	2		24	26		3	53
Montana												
Nebraska	7	3			8	1	1	4	5	1		10
Nevada												
New Hampshire	1				1			1				1
New Jersey	63	9		1	71	2		59	13	1	2	75
New Mexico												
New York	170	49	6	4	223	13	2	160	73	5	9	247
North Carolina	4	3		1	7	1		2	6		1	9
North Dakota	1				1			1				1
Ohio	30	42	1	1	65	9		22	51	1	4	78
Oklahoma	2	3			5			1	4			5
Oregon	8	4	1		13			9	4			13
Pennsylvania	100	65	6	2	163	8		80	90	1	3	174
Rhode Island	12				12			8	4			12
South Carolina	10	1			9	2		3	8			11
South Dakota												
Tennessee	17	3			20			14	6			20
Texas	24	15	1		35	5		25	15			40
Utah	12	2			13		1	11	3			14
Vermont	7				6	1		6		1		7
Virginia	18	15	1	2	28	8		9	27			36
Washington	20	8	1		25	4		8	21			29
West Virginia	7	4			10	1		8	3			11
Wisconsin	25	19	3		42	5		14	33		2	49
Wyoming												
Totals	1 0[illegible]0	3[illegible]0	37	19	1,340	103	13	704	643	19	35	1 491

STAFF CONFERENCES

That the staff conference has a definite place in the instruction of interns is shown by the fact that 1,376 interns reported that attendance at those meetings is compulsory This is encouraging, and it is felt that the number might be augmented had the thirty-one interns not answering the question done so

On this point, therefore, we feel that the Council's requirements are being substantially met While it is realized that only 493 of the 700 hospitals considered in this survey are approved for intern training, yet the 'Essentials in a Hospital Approved for Interns" are applicable to all hospitals assuming the duty of instructing interns

Clinical conferences and lectures though of unlimited value to interns, are not apparently, being utilized to the same extent as the staff conferences Only 881 of the 1,491 interns reporting received the benefits of those conferences, which must, of necessity, be educational in nature, 549 definitely reported nonattendance, while 61 failed to answer the question

SUPERVISION OF INTERNS

Another interesting analysis is that regarding the supervision of interns Apparently the majority of staff members are alert to the need of close supervision during the fifth year Following are some of the methods employed, as described by the former interns

'Completely supervised by chief of staff and various chiefs on services "

Daily ward rounds with visiting staff '

'By visiting men who are teachers in medical school.

Ward rounds personal instruction, weekly conferences, daily supervision of charts

By resident and visiting staff '

"By circulating staff '

TABLE 3—*Obstetric Training*

State	Number of Deliveries by Interns: Under 10	10 to 49	Over 50	None	Unanswered	Number of Deliveries Assisted In: Under 10	10 to 49	Over 50	Number Not Stated	None	Unanswered	Total Reports
Alabama	2	3	5		2	3	6		2		1	12
Arizona												
Arkansas		3	1					2	2			4
California	15	28	12	6	1	4	10	11	18	4	9	62
Colorado	3	4	4	5	1	3	1	3	5	4	1	17
Connecticut	1	13	12	1	2	2	11	5	6	2	4	29
Delaware	2	8				1	1	1	2			5
Dist Columbia	2	7	1	8		1	4	3	3	5	2	18
Florida		5	2	1			3		3	1	1	8
Georgia	2	8	6	8			3	1	12	3		19
Idaho	1								1			1
Illinois	18	46	21	34	6		4	47	57	11	6	125
Indiana	10	19	1	7			6	15	16			37
Iowa	3	7	2	6	2			8	10		2	20
Kansas	4	1		6	1			3	3	6		12
Kentucky	2	11		4		2	2	2	9	1	1	17
Louisiana	3	5	1	5	1		3	2	6	4		15
Maine		7					2		3		2	7
Maryland		14		15	3		6	3	9	11	3	32
Massachusetts	5	18	21	21	6	2	22	8	14	10	6	71
Michigan	18	21	3	10		2	10	19	14	7		52
Minnesota	2	18	5	6	1	3	6	9	13	1		32
Mississippi		1							1			1
Missouri	14	19	1	17	2	3	3	8	21	14	4	53
Montana												
Nebraska	5			4	1		2	1	4	1	2	10
Nevada												
New Hampshire		1									1	1
New Jersey	2	49	17	5	2	5	25	7	24	6	8	75
New Mexico												
New York	17	86	50	84	10	3	33	29	73	84	25	247
North Carolina	1	3		2	3		1	2	3	1	2	9
North Dakota		1						1				1
Ohio	16	36	10	11	5	3	10	24	25	9	7	78
Oklahoma	4			1			2	1	2			5
Oregon	4	6		2	1	1	1	7	4			13
Pennsylvania	14	110	35	7	8	6	61	35	54	7	8	174
Rhode Island			3	8	1		1	1	1	8	1	12
South Carolina	1	4		6	1			1	7	3		11
South Dakota												
Tennessee	3	10	6	1		1	7	2	8	1	1	20
Texas	13	9	9	9		2	10	12	13	2	1	40
Utah	3	7	2	1	1		4	3	5		2	14
Vermont	1	4		2			1	2	2	2		7
Virginia	4	13	2	14	3	3	5	4	14	8	2	36
Washington	9	13		6	1		2	10	12	3	2	29
West Virginia	2	8		1			3	2	4		2	11
Wisconsin	13	25	2	11		2	5	20	15	7		49
Wyoming												
Totals	217	641	274	334	65	52	282	317	499	2[illegible]	106	1 491

Unfortunately, however some adverse comments are noted

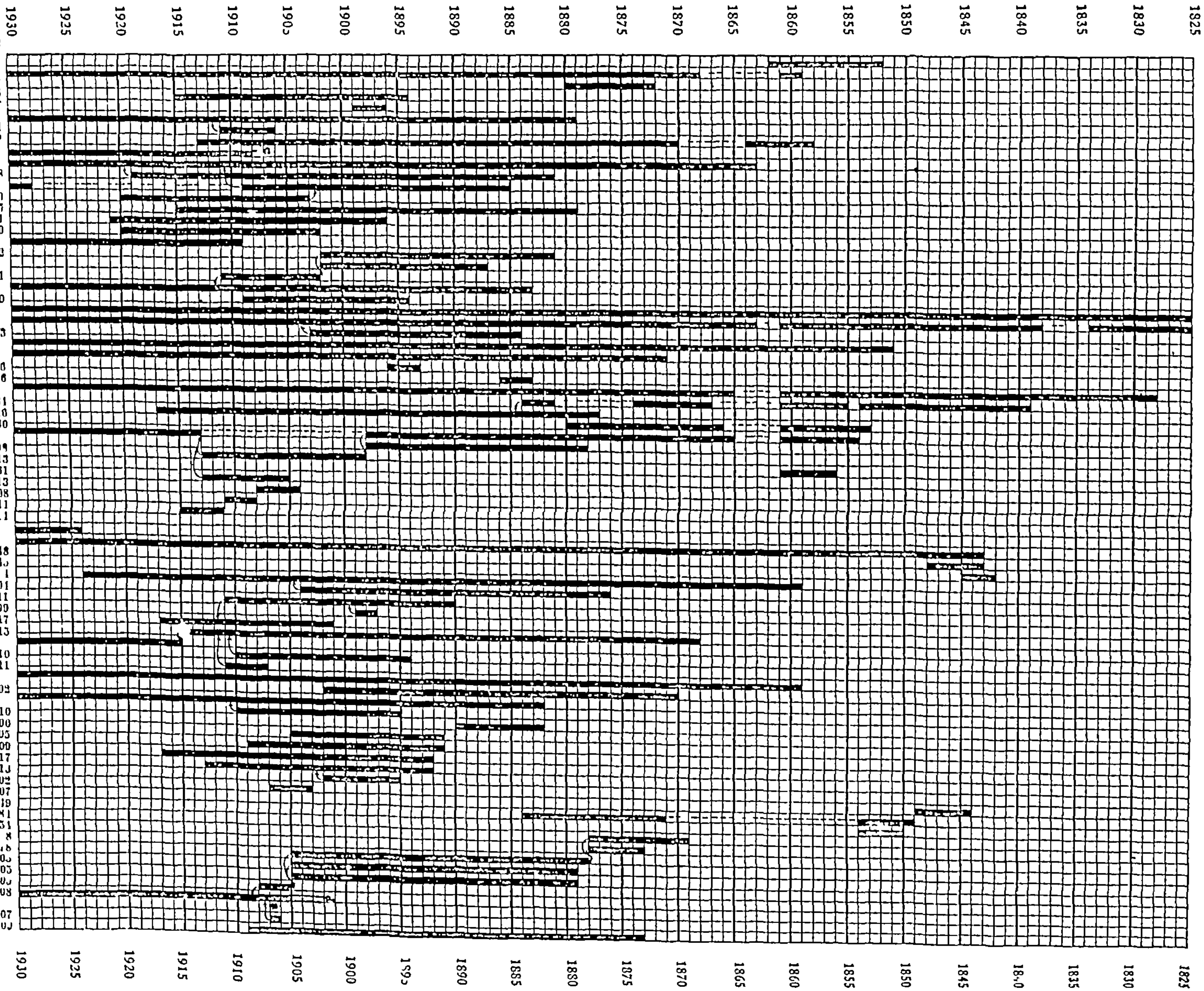
'An intern can do as much or as little work as he pleases the supervision is poor "

'Very poor supervision or none at all, sometimes interfered with by superintendent or nurses

"In no way except that chief intern requires that histories are taken

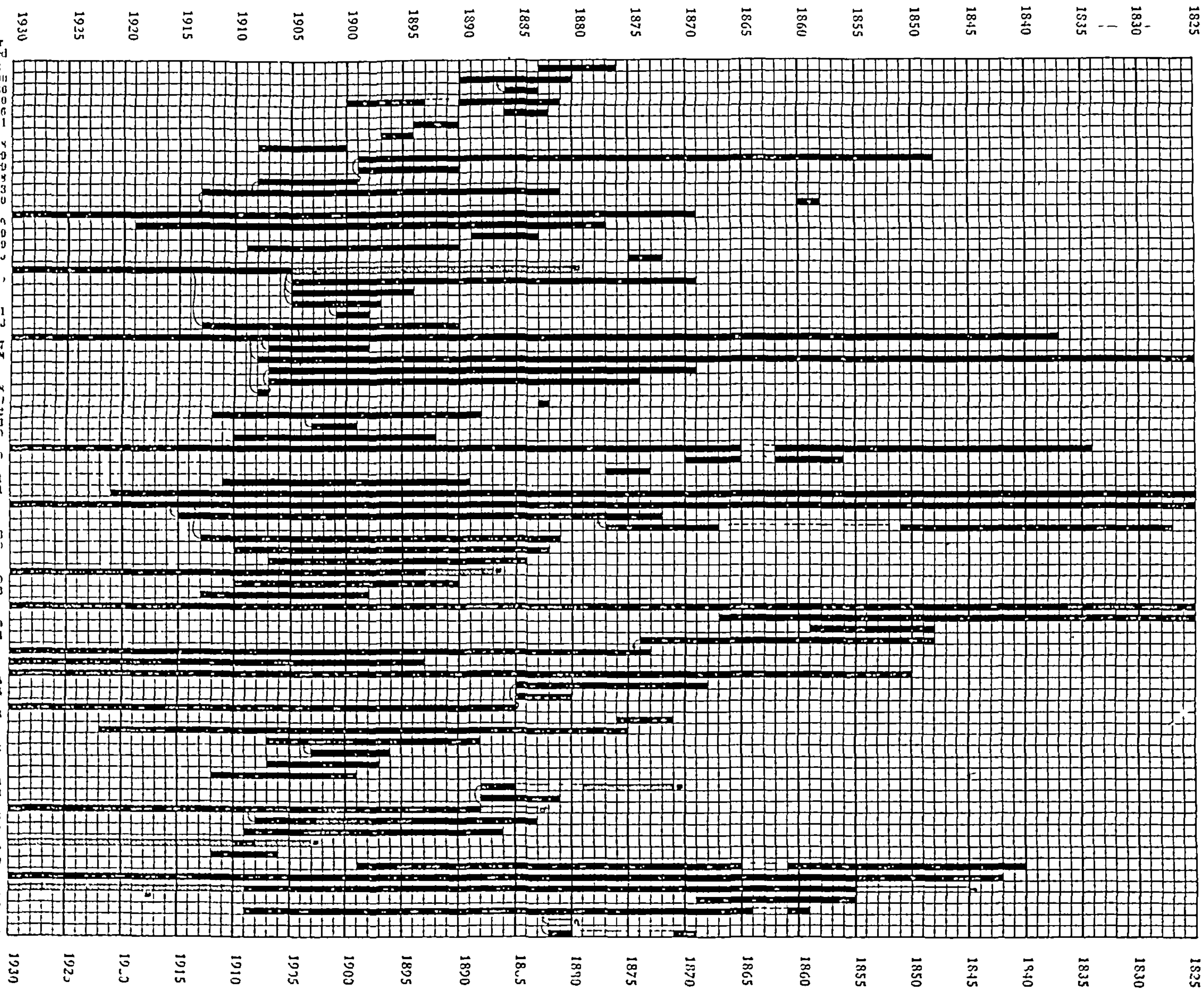
(Continued on page 514)

LIFE CHART OF THE MEDICAL COLLEGES OF THE UNITED STATES



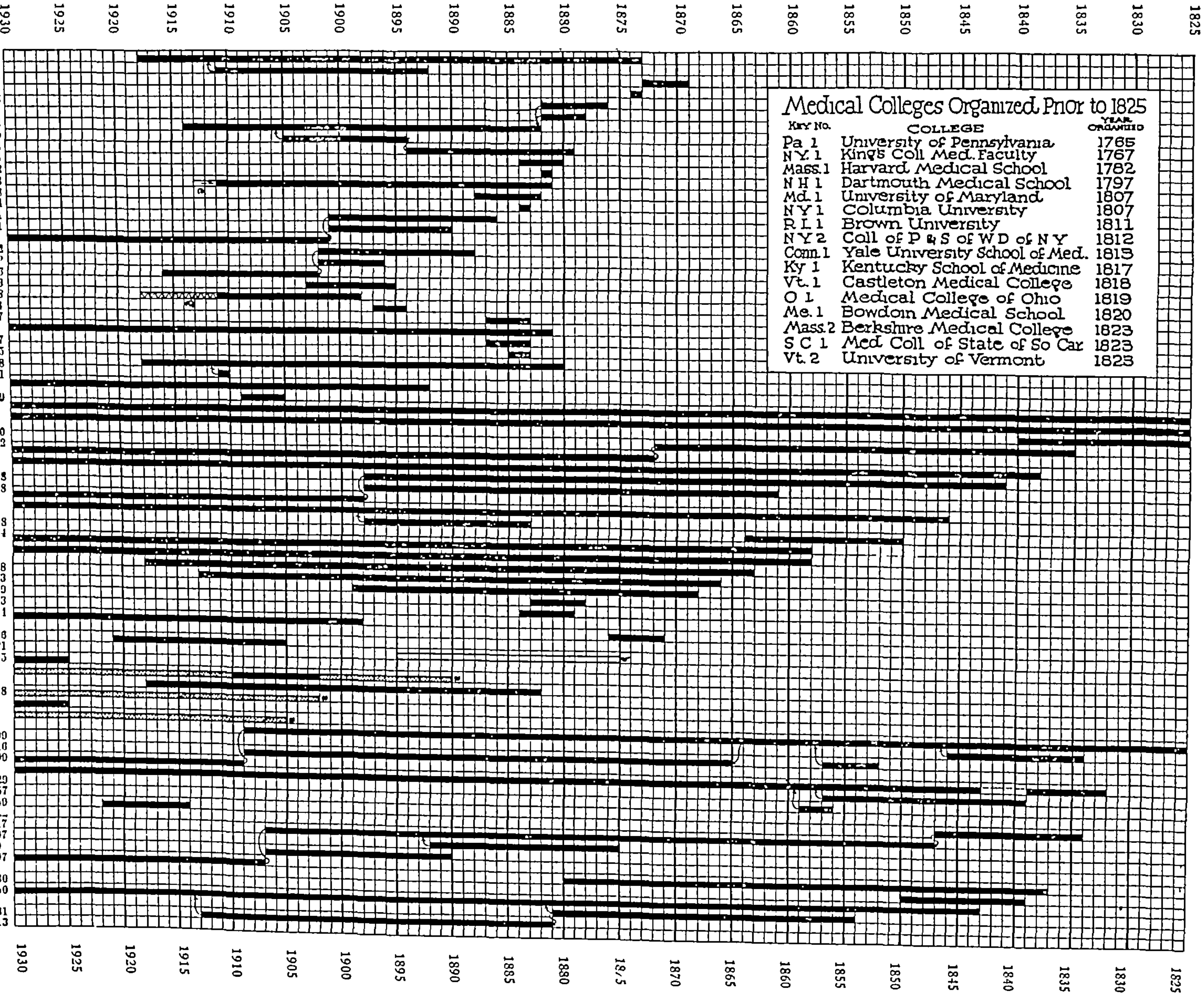
Key	No		Year Organized	Year Closed
Ala	1	Graffenburg Institute	1852	1861
Ala	2	U of Alabama	1859	
Ala	3	Southern Univ M D	1873	1880
Ala	4	Birmingham Med Coll	1894	1915
Ala	5	M C Montezuma Univ	1896	1899
Ark	1	U of Arkansas	1879	
Ark	2	C of P and S Little R	1906	1911
Cal	1	Cooper Med Coll	1858	1912
Cal	11	Stanford Univ	1908	
Cal	2	U of California	1863	
Cal	5	Hahne Med Coll	1881	1918
Cal	6	U of So Calif	1885	
Cal	9	C of P and S L A	1903	1920
Cal	4	Calif Eclec M C	1879	1915
Cal	7	C of P and S S F	1896	1921
Cal	8	Oakland C of M and S	1902	1920
Cal	12	Coll of Med Evan	1909	
Colo	1	Denver Coll of Med	1881	1902
Colo	3	Gross Med Coll	1887	1902
Colo.	5	Denver and Gross Coll	1902	1911
Colo.	2	U of Colorado	1883	
Colo	4	Denver C of P and S	1894	1909
Conn	1	Yale University	1813	
D C	1	Geo Wash University	1825	
D C	4	Natl Univ M D	1884	1903
D C		Georgetown Univ	1851	
D C	3	Howard Univ	1869	
D C	5	Wash Homeo M C	1893	1896
Fla	1	Tallahassee C M and S	1883	1886
Ga	1	U of Georgia	1829	
Ga	2	So Botan M C	1839	1881
Ga	3	Ga C Eclec M and S	1877	1916
Ga	4	Savannah Med Coll	1853	1880
Ga		Emory University	1854	
Ga	10	So Med Coll	1878	1898
Ga	11	Atlanta C P and S	1898	1913
Ga	6	Oglethorpe M C	1856	1861
Ga	12	Atlanta S of M	1905	1913
Ga	1	International M M C	1904	1908
Ga	18	Hosp M C Eclec	1908	1911
Ga	19	So C M and S	1911	1914
Ill	1a	Ogden G S of M (U of Chi)	1921	
Ill	1	Rush Medical Coll	1843	
Ill	2	M D Illinois Coll	1843	1848
Ill	3	Franklin M C	1842	1845
Ill	4	General Med Coll	1850	1921
Ill	10	Chi Homeo M C	1876	1904
Ill	5	C M and S (Phy Med)	1883	1911
Ill	20	Chi C M and S (Phy Med)	1897	1899
Ill	22	Chi C M and S	1901	1917
Ill	8	Bennett Med Coll	1868	1915
Ill	43	Loyola University	1915	
Ill	17	Illinois Med Coll	1894	1910
Ill	39	Reliance Med Coll	1907	1911
Ill	6	Northwestern Univ	1859	
Ill	9	No Univ Wo M C	1870	1902
Ill	11	U of Illinois	1882	
Ill	19	Amer M Miss Coll	1895	1910
Ill	12	Chaddock Sch of Med	1889	1890
Ill	13	Harvey Med Coll	1891	1905
Ill	14	Natl Med Univ	1891	1909
Ill	16	Jenner Med Coll	1893	1917
Ill	15	Hering Med Coll	1892	1913
Ill	18	Dunham Med Coll	1895	1902
Ill	3	Dearborn Med Coll	1903	1907
Ind	1	Indiana Med Coll	1845	1849
Ind	2	Med Coll of Evansville	1849	1854
Ind	3	Ind Cent Med Coll	1850	1851
Ind	4	Ind Med Coll Indianapolis	1869	1878
Ind	6	C of P and S of Ind	1873	1878
Ind	8	Med Coll of Indiana	1878	1905
Ind	9	Cent Coll P and S	1879	1905
Ind	10	Fort Wayne C of M	1879	1905
Ind	18	Ind Med Coll Purdue U	1905	1908
Ind	0	Indiana University	1903	
Ind	1	State C of P and S	1906	1907
Ind	5	Physio Med College	1873	1909

	Key No		Year Organized	Year Closed
Ind	7	Med Coll of Fort Wayne	1876	188
Ind	11	Ind Eclec Med Coll	1880	1890
Ind	11	Beach Med Institute	1883	1880
Ind	12	Curtis Phy Med Inst	1881	1900
Ind	13	Hosp Med Coll Evans	1882	1886
Ind	16	Eclec Coll P and S	1890	1891
Ind	19	American Med Coll	1901	189
Ind	1	Eclec Med Coll	1900	1908
Ia	1	C of P and S Keokuk	1849	1899
Ia	9	Keokuk Medical College	1890	1899
Ia	10	Keo M C C of P and S	1899	1908
Ia	6	Drake University	1881	1913
Ia	2	Iowa Medical College	18 8	1860
Ia	3	State Univ of Iowa	1869	
Ia	5	State U of Iowa Col Homeo	18	1919
Ia	7	King Eclec Med Coll	1883	1890
Ia	8	Sioux City C of M	1890	1909
Kan	1	Kansas Med Coll	187	18
Kan	2	Univ of Kansas	1880	
Mo	8	Kansas City Med Coll	1869	1905
Kan	1	Col P and S Kansas City	1894	190
Mo	3	Med Chir C of Kansas City	1897	190
Mo	11	Columbian Med Coll	1898	1901
Kan	4	Kansas Medical Coll	1890	1913
Ky	2	Univ of Louisville	1837	
Ky	9	Kentucky Univ M D	1898	1907
Ky	1	Ky Sch of Med	1917	1908
Ky	1	Louisville Med Coll	1869	190
Ky		Hosp Coll of Med	1874	190
Ky	11	Louisville and H M C	1907	1908
Ky	6	*Jefferson Sch of Med*	188	188
Ky		*Louis Natl Med Coll*	1888	1912
Ky	10	M D State U Louisville	1899	1903
Ky	8	So West H M C	189	1910
La	1	Tulane University	1834	
La	2	New Orleans S of M	1856	18 0
La	3	Char H Med Coll	18 3	18
La	4	Flint Med Coll	1889	1911
Me	1	Bowdoin Med Sch	18 0	1921
Md	1	Univ of Maryland	1807	
Md	3	C of P and S Baltimore	18	191
Md	2	Washington Univ	18	18
Md	4	Baltimore Med Coll	1881	1913
Md	5	Woman's Med Coll	1882	1910
Md	6	Baltimore University	1884	190
Md		Johns Hopkins Univ	188	
Md	8	Atlantic Med Coll	1890	1910
Md	9	Maryland Med Coll	1898	1913
Mass	1	Harvard Med Sch	1 8	
Mass	2	Berkshire Med Coll	18 3	188
Mass	1	Worcester Med Coll	1848	18 0
Mass	3	New Eng Female M C	1848	18 4
Mass	5	Boston University	18 3	
Mass		Tufts Coll Med Sch	1893	
Mich	1	Univ of Michigan M S	18 0	
Mich	2	Detroit Med Coll	1868	1885
Mich	6	Michigan Coll of Med	1880	1885
Mich		Detroit C M and S	18	
Mich	3	Detroit Homeo M C	18 1	18 6
Mich	5	Univ of Mich Homeo M S	18 5	19
Mich	8	Mich C M and S	1888	190
Mich	9	Saginaw Valley M C	1896	1903
Mich	10	Grand Rapids M C	18	190
Mich	11	Detroit Homeo Coll	1899	191
Minn	1	St Paul Med Coll	18 1	1888
Minn	2	Minnesota Hosp Coll	1881	1 8
Minn	4	Univ of Minnesota	1883	
Minn	5	Minneapolis C P and S	1883	1 08
Minn	6	U of Minn Homeo	18	1909
Mi	1	U of Mississippi	1903	
Miss	2	Mississippi M C	1906	191
Mo	1	M [illegible] Med Coll	1840	189
M	2	Washington Univ	184	
Mo	3	U of Missouri	184	
Mo	4	H [illegible] Med Coll	18	1
Mo	5	H [illegible] M C of Mo	1 9	190
Mo	1	[illegible] Med Coll	18 0	188
Mo		St Louis C Homeo [illegible]	1 69	188



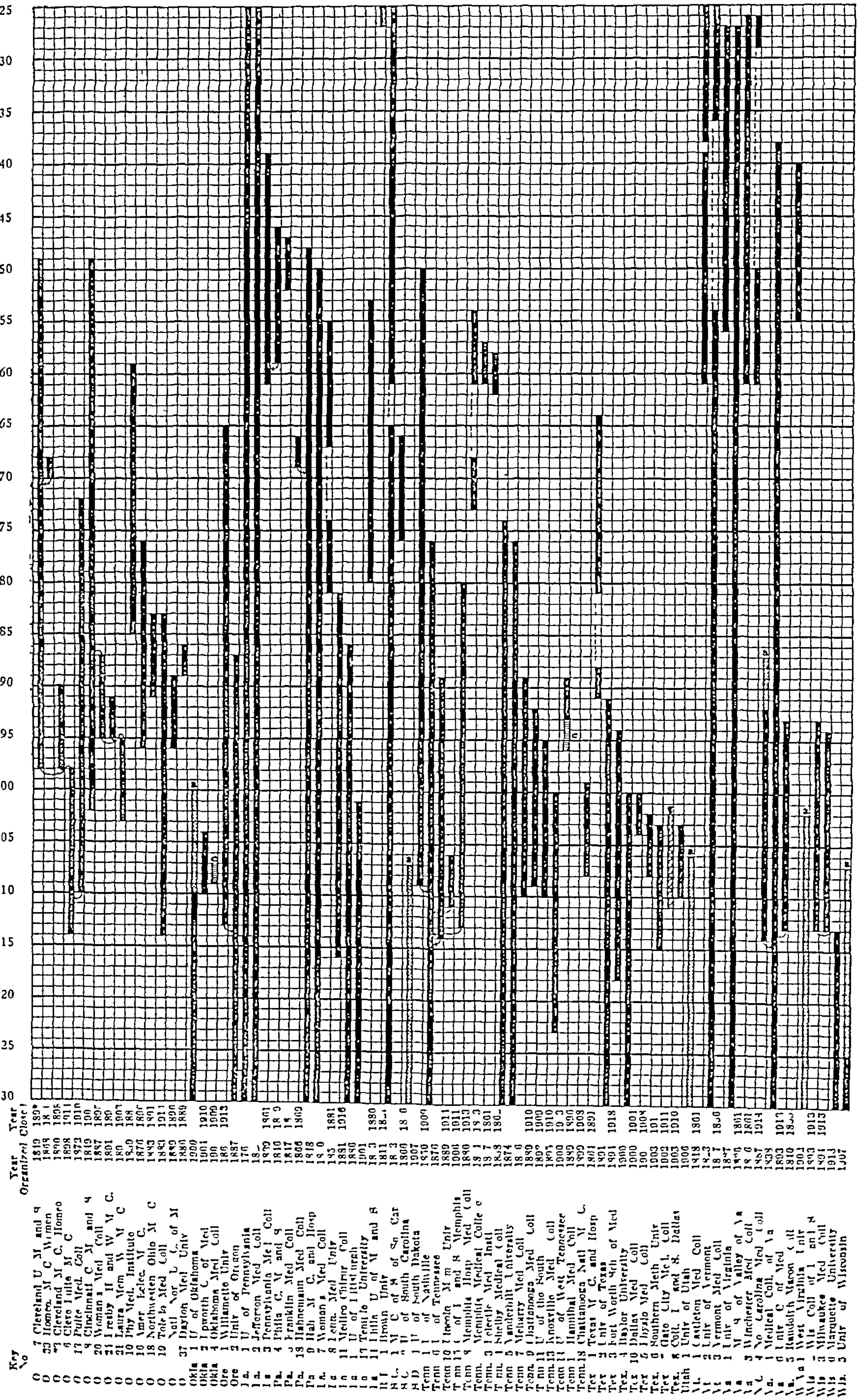
LIFE CHART OF THE MEDICAL COLLEGES OF THE UNITED STATES—*Continued*

Key No.			Year Organized	Year Closed
Mo.	10	Natl U Arts and Sciences	1873	1918
Mo.	28	Barnes Med Coll	1892	1911
Mo.	11	Med Coll Kans City	1869	1873
Mo	12	St. Louis Hahne M C	1873	1874
Mo.	14	St. Louis Hosp M C.	1876	1882
Mo	15	C of P and S St. Jos	1878	1882
Mo	22	Ensworth Med Coll	1883	1914
Mo.	20	Central M. C. St Jos	1894	1905
Mo	18	Northwestern Med Coll	1879	1894
Mo.	17	Joplin C. of P and S	1880	1884
Mo.	19	Joplin Med. Coll	1881	1882
Mo.	20	Univ Med Coll. Kans City	1881	1913
Mo	21	Kans City Hosp C. of M	1882	1888
Mo	23	Woman's Med Coll	1883	1884
Mo	1	Beaumont Hosp Med Coll	1886	1901
Mo	27	Marion Sims C of M	1890	1901
Mo	31	St. Louis University	1901	
Mo	26	Kans City Homeo M C	1888	1902
Mo	31	Hahnemann M C.	1896	1902
Mo	35	Southwest S. of M	1902	1916
Mo	30	Woman's M Col Kan City	1895	1903
Mo	33	Eclectic Med. Univ	1898	1918
Mo	37	St L. Woman's M C	1894	1896
Neb	1	U of Nebraska Lincoln	1883	1887
Neb	5	U of Nebraska Omaha	1881	
Neb	3	U Nebr C of M Homeo	1883	1887
Neb	2	U Nebr Eclec. Dept	1883	1885
Neb	4	Lincoln Med Coll	1890	1918
Neb	8	Nebr Med. Coll	1910	1911
Neb	6	Creighton University	189	
Neb	7	Nebraska C of M	190	1909
N H.	1	Dartmouth Med. Sch	1797	
N Y	1	Columbia University	1807	
N Y	2	C. of P and S of W D	1812	1840
N Y	4	Geneva Medical College	1835	1872
N Y	15	Syracuse University	1872	
N Y	3	Albany Med Coll	1838	
N Y	5	New York Univ M D	1841	1898
N Y	10	Bellevue Hosp M C.	1861	1898
N Y	10	U and Bellevue H M C.	1898	
N Y	6	Univ of Buffalo	1846	
N Y	18	Niagara University	1883	1898
N Y	7	New York Med. Coll	1850	1864
N Y	8	Long Island Coll Hosp	1858	
N Y	9	N Y Homeo M C.	1858	
N Y	11	N Y M C and H for Wo	1863	1918
N Y	13	Eclectic M C. of C of N Y	1866	1913
N Y	14	W M C. of N Y I for W C	1868	1899
N Y	16	U S Med Coll	1878	1883
N Y	17	C. of P and S Hom Buff	1879	1881
N Y	40	Cornell University	1898	
N Y	3	N Y Free M C for Wo	1871	1876
N Y	43	Fordham University	1905	1921
N Y	1	Reg U of S of N Y	1875	1895
N Y	15	Univ of Rochester	1925	
N C	1	U of North Carolina	1890	
N C.	3	Leonard Med Sch	1882	1918
N C	5	Wake Forest Coll	1902	
N C.	7	Duke University	1925	
N D	1	Univ of North Dakota	1905	
O	1	Medical Coll. of Ohio	1819	1909
O	[illegible]	Cincinnati Med. Coll	1834	1840
O	9	Miami Med Coll	1852	1909
O	41	U of Cincinnati	1909	
O		Eclec. Med. Coll	1833	1929
O	30	Amer M C. Eclec	1839	1857
O	31	Eclec C. of M and S	1856	1859
O	42	Ohio State Univ Homeo	1914	1922
O	28	Willoughby Univ	1835	1847
O	3	Starling Med Coll	1847	1907
O	14	Columbus Med Coll	1875	189
O	25	Ohio Med. Univ	1890	1907
O	40	Ohio State Univ	1907	
O	4	Physio Med Coll	1836	1880
O	5	Botan Med. Coll	1838	1850
O	6	West. Reserve Univ	1843	
O	11	Univ of Wooster	1864	1881
O	12	Cleveland C. of P S.	1881	1913



Medical Colleges Organized Prior to 1825

Key No.	College	Year Organized
Pa. 1	University of Pennsylvania	1765
N.Y. 1	Kings Coll. Med. Faculty	1767
Mass. 1	Harvard Medical School	1782
N H 1	Dartmouth Medical School	1797
Md. 1	University of Maryland	1807
N Y 1	Columbia University	1807
R I 1	Brown University	1811
N Y 2	Coll of P & S of W D of N Y	1812
Conn. 1	Yale University School of Med.	1813
Ky 1	Kentucky School of Medicine	1817
Vt. 1	Castleton Medical College	1818
O 1	Medical College of Ohio	1819
Me. 1	Bowdoin Medical School	1820
Mass. 2	Berkshire Medical College	1823
S C 1	Med. Coll. of State of So Car	1823
Vt. 2	University of Vermont	1823



1825— 17
1826— 19
1827— 21
1828— [illegible]
1829— 21
1830— 21
1831— 21
1832— [illegible]
1833— 22
1834— 24
1835— 25
1836— 25
1837— 26
1838— 29
1839— 32
1840— 33
1841— 34
1842— 36
1843— 40
1844— 41
1845— 41
1846— 42
1847— 43
1848— 46
1849— 48
1850— 53
1851— 53
1852— 54
1853— 56
1854— [illegible]
1855— 59
1856— 61
1857— 60
1858— 65
1859— 67
1860— 68
1861— 51
1862— 47
1863— 50
1864— 49
1865— 58
1866— 62
1867— 61
1868— 68
1869— 72
1870— 71
1871— 76
1872— 80
1873— 84
1874— 84
1875— 86
1876— 89
1877— 89
1878— 91
1879— 97
1880—100
1881—100
1882—111
1883—122
1884—110
1885—110
1886—120
1887—123
1888—121
1889—127
1890—133
1891—135
1892—140
1893—145
1894—152
1895—[illegible]
1896—151
1897—155
1898—156
1899—151
1900—158
1901—157
1902—159
1903—[illegible]
1904—155
1905—158
1906—160
1907—157
1908—150
1909—140
1910—130
1911—[illegible]
1912—118
1913—101
1914—100
1915— 95
1916— 93
1917— [illegible]
1918— 81
1919— 82
1920— [illegible]
1921— 77
1922— 75
1923— [illegible]
1924— [illegible]
1925— [illegible]
1926— [illegible]
1927— 76
1928— [illegible]
1929— [illegible]

(Continued from page 509)

"Only as the attending physicians see fit to do so on the various services"

Since the intern should be allowed initiative only under supervision, it is of vital importance that all physicians responsible for the training of interns should perform this additional duty in the best interests of the young physician

SURGICAL DEPARTMENT

Following the four years in medical college the graduate is naturally anxious, in his fifth year in medicine, to correlate in a more definite manner the theoretical with the practical, to demonstrate, still further, the extent to which the theories with which he has familiarized himself are applicable Perhaps this urge is most strongly felt in the field of surgery Before being permitted to attempt the real surgical procedures, however, minor or major, it is again emphasized, as in the "Essentials," that skill in diagnosis and postoperative treatment be the first objective This is a stepping stone, as it were, to a first assistantship in the operating room, later, with discretion and under the most rigid supervision, surgical procedures may be entrusted to him

The logic of this procedure, its practicability and efficacy, are unquestioned, yet we find a seemingly greater divergence in the reports on surgical services than elsewhere in these tabulations Fifty-three per cent of the interns reporting were permitted to do major surgery—indeed, some of the operations described would seem to require more mature skill, 90 per cent were allowed to perform minor surgery, and 70 per cent acted as first assistants The reports appear to be unanimous in stating that major surgery is permitted only under strict supervision, which is, of course, as it should be

TABLE 4—*Anesthetics Given by Interns*

State	In Surgical Department					In Obstetrical Department				
	Many	Few	None	Unanswered	Total	Many	Few	None	Unanswered	Total
Alabama	7	3	1	1	12	5	4	2	1	12
Arizona										
Arkansas	4				4	4				4
California	37	9	15	1	62	40	12	10		62
Colorado	12	3		2	17	14		2	1	17
Connecticut	21	3	3	2	29	17	5	2	5	29
Delaware	5				5	3	2			5
Dist Columbia	7	5	5	1	18	9	2	7		18
Florida	6	2			8	3	5			8
Georgia	11	2	5	1	19	14	1	2	2	19
Idaho	1				1			1		1
Illinois	84	7	25	9	125	74	19	28	4	125
Indiana	37				37	27	5	3	2	37
Iowa	12	3	4	1	20	11	5	2	2	20
Kansas	8	3	1		12	3	2	7		12
Kentucky	15	2			17	11	2	3	1	17
Louisiana	7	4	3	1	15	5	4	6		15
Maine	4	1	2		7	1	2	2	2	7
Maryland	24		6	2	32	15	4	10	3	32
Massachusetts	50	4	11	6	71	34	9	23	5	71
Michigan	31	6	13	2	52	28	8	14	2	52
Minnesota	11	5	16		32	11	6	15		32
Mississippi	1				1			1		1
Missouri	32	10	7	4	53	25	8	17	3	53
Montana										
Nebraska	5	2	1	2	10	4	2	2	2	10
Nevada										
New Hampshire			1		1			1		1
New Jersey	62	5	5	3	75	53	9	4	9	75
New Mexico										
New York	158	26	37	26	247	122	20	91	14	247
North Carolina	6		3		9	4	2	2	1	9
North Dakota			1		1			1		1
Ohio	40	11	21	6	78	44	8	19	7	78
Oklahoma	4	1			5	3		2		5
Oregon	5	2	5	1	13	5	6	2		13
Pennsylvania	151	8	6	9	174	104	36	17	17	174
Rhode Island	7	1	2	2	12	4		8		12
South Carolina	9	1		1	11	6	2		3	11
South Dakota										
Tennessee	13	6	1		20	13	1	5	1	20
Texas	27	7	5	1	40	26	7	6	1	40
Utah	12	1		1	14	5	5	1	3	14
Vermont	7				7	5		2		7
Virginia	23	6	7		36	13	9	10	4	36
Washington	11	7	10	1	29	10	8	10	1	29
West Virginia	10	1			11	6	4		1	11
Wisconsin	25	12	12		49	19	13	17		49
Wyoming										
Totals	1 002	169	234	86	1 491	800	237	357	97	1 491

TABLE 5—*Arrangement of Services of Interns*

State	Rotating	Straight	Services Not Divided	Unanswered	Total
Alabama	9	3			12
Arizona					
Arkansas	3			1	4
California	58	3		1	62
Colorado	14	3			17
Connecticut	24	4		1	29
Delaware	4	1			5
District of Columbia	13	4		1	18
Florida	7	1			8
Georgia	14	5			19
Idaho		1			1
Illinois	102	23			125
Indiana	33	4			37
Iowa	15	5			20
Kansas	10	2			12
Kentucky	10	6		1	17
Louisiana	10	5			15
Maine	6	1			7
Maryland	18	14			32
Massachusetts	44	20	6	1	71
Michigan	46	2	4		52
Minnesota	29	1	2		32
Mississippi	1				1
Missouri	39	8	6		53
Montana					
Nebraska	8		1	1	10
Nevada					
New Hampshire	1				1
New Jersey	68	3	3	1	75
New Mexico					
New York	176	64	3	4	247
North Carolina	5	2	1	1	9
North Dakota	1				1
Ohio	69	7		2	78
Oklahoma	5				5
Oregon	13				13
Pennsylvania	161	11	1	1	174
Rhode Island	7	4		1	12
South Carolina	8			3	11
South Dakota					
Tennessee	15		2	3	20
Texas	35	1	3	1	40
Utah	10		2	2	14
Vermont	7				7
Virginia	29	1	5	1	36
Washington	24	3	1	1	29
West Virginia	10	1			11
Wisconsin	34	6	8	1	49
Wyoming					
Totals	1 195	219	48	29	1 491

That a majority of the interns reporting indicate they are allowed to perform major surgery, even under supervision, at first glance is surprising, if not alarming However, it is quite likely that if only those hospitals approved for interns by the Council were considered, this figure would be materially lower Another factor to be considered is that many of the interns reporting doing major surgery have in all probability really been allowed very few such operations, and those operations were doubtless appendectomies, herniotomies or other common procedures Nevertheless, the idea, apparently growing, that interns are in the hospital primarily to acquire surgical technic and become surgeons should be discouraged without additional graduate preparation in that subject

One hundred and three interns reported receiving no experience in minor surgery and 643 none in major surgery

The intern should receive instruction and experience in the administration of the various kinds of anesthetics during his hospital year, however, in the surgical department 234 interns reported no experience in anesthesia, as compared with 1,002 who administered "a good many" anesthetics, and 169 "a few"

OBSTETRIC DEPARTMENT

In the department of obstetrics the majority of interns apparently received adequate experience For the purpose of calling special attention to this service, the following figures are abstracted from the table

Deliveries	Full Charge	Assisted in
Under 10	217	52
10-49	641	282
Over 50	234	317

An additional 499 interns reported assisting at deliveries but did not specify the exact number

In contrast with these figures, it is surprising to note that 334 interns were not permitted to assume charge of any deliveries, and 235 did not even have the opportunity of assisting at deliveries We have included in these totals reports sent us by interns on a straight service

Figures indicating the number of anesthetics given by interns on the obstetric service are also included in the accompanying table

Table 6—*Writing of Histories*

State	For All Patients	For Some Patients	None	Unanswered	Total
Alabama	12				12
Arizona					
Arkansas	3	1			4
California	62				62
Colorado	13	4			17
Connecticut	27	2			29
Delaware	5				5
District of Columbia	15	2	1		18
Florida	8				8
Georgia	17		2		19
Idaho	1				1
Illinois	124			1	125
Indiana	35	1	1		37
Iowa	20				20
Kansas	11	1			12
Kentucky	16	1			17
Louisiana	15				15
Maine	7				7
Maryland	27	4		1	32
Massachusetts	67	4			71
Michigan	52				52
Minnesota	32				32
Mississippi		1			1
Missouri	53				53
Montana					
Nebraska	10				10
Nevada					
New Hampshire	1				1
New Jersey	72	3			75
New Mexico					
New York	233	12	1	1	247
North Carolina	8	1			9
North Dakota	1				1
Ohio	74	2	1	1	78
Oklahoma	5				5
Oregon	13				13
Pennsylvania	168	6			174
Rhode Island	7	5			12
South Carolina	11				11
South Dakota					
Tennessee	15	5			20
Texas	35	2	3		40
Utah	14				14
Vermont	7				7
Virginia	36				36
Washington	27	1	1		29
West Virginia	10	1			11
Wisconsin	44	5			49
Wyoming					
Totals	1 413	64	10	4	1 491

TYPE OF SERVICE

A continuation of the study of 1,491 reports received discloses that 1,195 interns obtained a rotating service, 219 a straight service, 48 stated that no definite form of service was provided, while 29 failed to answer the question It will be noted at a glance, therefore, that the rotating type of intern service because of its rather general acceptance, is conceded to have certain advantages over the straight service Attention is called however, to two outstanding exceptions Maryland and Massachusetts Eighteen interns reported a rotating service in hospitals in the former state as compared with 14 obtaining straight service, the tabulation for Massachusetts shows 44 interns receiving a rotating service, 20 a straight service Noteworthy, also, are the figures for New York state where the percentage is 71 for the rotating system and 26 for the straight, with seven hospitals left unclassified

Table 7—*Physical Examinations*

State	On All Ward Patients	On Some Ward Patients	None	Unanswered	On All Private Patients	On Some Private Patients	None	Unanswered
Alabama	12				3	2	3	4
Arizona								
Arkansas	4				1	2	1	
California	5	2	1	2	12	20	17	3
Colorado	12	2		2	6	3	6	2
Connecticut	25				10	11	2	
Delaware	5				4	1		
District of Columbia	17		1		6	8	3	1
Florida	8				1	4	1	2
Georgia	19				11	3	3	2
Idaho	1				1			
Illinois	114	1		10	101	15		6
Indiana	31	1		5	27	9	1	
Iowa	18	1		1	12	7		1
Kansas	10	2			9	3		
Kentucky	16	1			4	8	2	3
Louisiana	14	1			10	1	3	1
Maine	7				2	3	1	1
Maryland	31			1	10	2	3	8
Massachusetts	63			2	14	25	29	3
Michigan	50			2	44	2		6
Minnesota	23		1	3	24	4		4
Mississippi	1				1			
Missouri	52	1			31	5	1	16
Montana								
Nebraska	9	1			7	2		1
Nevada								
New Hampshire	1					1		
New Jersey	75				40	19	11	5
New Mexico								
New York	242	1	1	3	103	51	33	60
North Carolina	8	1			6	2	1	
North Dakota	1					1		
Ohio	78				54	11	7	6
Oklahoma	5				3	2		
Oregon	12			1	9	2		2
Pennsylvania	174				121	38	6	9
Rhode Island	12				1	7	2	2
South Carolina	11				8	3		
South Dakota								
Tennessee	10			1	11	7	4	2
Texas	38			2	25	6		9
Utah	14				10	3	1	
Vermont	7				7			
Virginia	28			8	26	5	5	
Washington	20	1		6	13	7		9
West Virginia	10			1	7	3	1	
Wisconsin	45	1		3	42	4	1	2
Wyoming								
Totals	1 415	17	4	55	865	305	148	170

HISTORIES

It would seem that the vast majority of the hospitals appreciate the value to the intern of history taking, since 1 413 interns were permitted to take histories of all patients on their service, thus illustrating the rather strict adherence, in this particular, to the Council's "Essentials" An additional 64 interns recorded some histories 10 stated that no histories were required, and 4 failed to reply While this total of 78 might seem negligible, yet it is particularly important that at this period of every young physician's training emphasis should be placed on the necessity of securing accurate and complete histories

PHYSICAL EXAMINATIONS

Another duty devolving on the intern is the physical examination of patients in his service, and this does not

that the pulmonary changes comprise diffuse bronchiolitis and peribronchial cellular infiltrations causing scattered, focal pneumonic lesions

Therapeutic Features—Since Weingarten (1943) reported his chance cure of this syndrome with arsphenamine, oral and intravenous medication with organic arsenicals have become so well established as almost to constitute a therapeutic test

After adequate trial of various schemes of treatment, both oral and parenteral, I have reached the conclusion that effective control of the condition can be established in the majority of cases with a ten-day course of oral therapy divided into two stages of four and six days separated by a two-day interval Good results have been achieved with a dosage of one 0 25 gm tablet of carbarsone given twice daily after meals, involving a total ingestion of 1 44 gm of arsenic A Herxheimer reaction frequently occurs between the third and fifth days of treatment, with clinical exacerbation, sometimes producing status asthmaticus, and an eosinophilic increase This almost invariably presages a rapidly effective therapeutic response

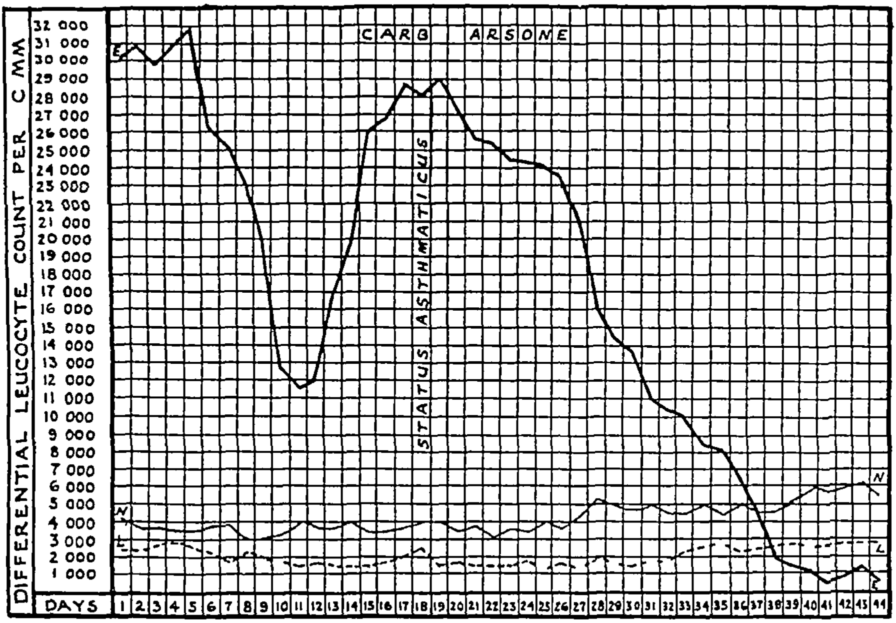


Fig 3—Eosinophilic Respiratory Syndrome Differential leucocyte chart showing eosinophilic reaction (E) before, during and after ten days' arsenical therapy, with no associated disturbance of neutrophils (N) and lymphocytes (L)

Gastrointestinal, hepatic, encephalitic and other complications of arsenical medication have been conspicuously absent in my personal experience, this might, possibly, be attributable to adherence to a restricted schedule of administration of arsenic and strict enforcement of rest during treatment

Origin of the Syndrome

What remains unknown about the origin of this syndrome may be even more significant than what is known about its nature A few suggestive observations gathered from ætiological study may be correlated with clues to the pathogenesis detected by laboratory search

Age, sex and race have no ætiological significance other than might be incidental to environment The possible significance of environment was suggested by the observation that 80 out of 100 cases studied in Ceylon (Soysa, 1949) showed evidence of exposure to inhalation of airborne mites in dusty stores, warehouses, mills, etc

Possible ætiological factors suggested by results of laboratory investigations include pulmonary helminthiasis, pulmonary spirochætosis, pulmonary filariasis, pulmonary virus infection and pulmonary acariasis

Observations in Ceylon, initiated by the work of Carter, Wedd and D'Abrera (1944) have resulted in the isolation from the sputum of various mites in all stages of their life cycle The mites most frequently found were species of *Tyroglyphus*, *Tarsonemus*, *Glyciphagus* and *Carpoglyphus* Carter and D'Abrera (1946) have found a significant reduction of mites in the sputum of patients after arsenical treatment The search for mites is a painstaking task An equally painstaking search in controls revealed no mites in the sputum of healthy subjects, and cases of non-eosinophilic respiratory disorders (Soysa, 1949) The relatively scanty numbers of mites found in the sputum in this syndrome is comparable to the paucity of mites in cutaneous acariasis, such as scabies and acarine dermatoses, the symptoms in both instances being out of all proportion to the meagre number of mites found

Mites have been isolated in cases of gastritis, diarrhœa, cystitis, scrotal cyst, lung abscess, cancer, etc They have been suspected as pathogenic agents in asthma long ago, so that the recently postulated link between airborne mites and the eosinophilic respiratory syndrome is not an entirely new concept It is, however, impossible, at this stage, to be certain that mites, even when found, are responsible either for the eosinophilia or the respiratory disturbance But, although the syndrome continues to defy precise pathological definition, it appears to be associated with a multiple ætiology in which mites may have a possible role

REFERENCES

Carter, H F, and D'Abrera, V St E (1946), *Trans Roy Soc Trop Med and Hyg*, 39, 373
Carter, H F, Wedd, G, and D'Abrera, V St E (1944), *Ind Med Gaz*, 79, 163
De Langen, C D, and Djamil, M (1923), *Genesk tijdschr Med Ind*, 63, 406
Meyenburg, H (1942), *Schweiz Med Woch*, 72, 809
Soysa, E (1949), *Journ Roy Army Med Cps*, 92, 1
Soysa, E, and Jayawardena, M D S (1945), *Brit Med Journ* 1, 1
Viswanathan, R (1947), *Journ Trop Med*, 50, 93
Weingarten, R J (1943), *Lancet*, 1, 103
Wilson, H (1950), *Trans Roy Soc Trop Med and Hyg*, 44, 256

THE HISTORY OF HUMAN CANCER

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SUCH compelling circumstances and instincts as want and fear exercised man's faculties and determined his actions Medical knowledge evolved gradually as a part of corrective and, later, preventive measures to meet the hazards of man's life Our present-day knowledge, in its ultimate analysis, may be regarded as our heritage from successive interacting cultures The earliest medical records are found in Shen Nung's comprehensive Herbal in China,[1] the Brahmin legendary records in India [2] and the knowledge of Taaut, engraved upon the columns and collected in papyri in Egypt [3] These records appear to be equally remote in antiquity (*circa* B C 2500), yet each has its own distinctive features, suggesting the existence of earlier, extinct or even forgotten civilisations The social advancement of these cultures was generally co-ordinated and disciplined by priestly castes, who, though often exploiting public ignorance, laid the foundations of medical aid and hygiene The separation of rationalism from mysticism during ancient Greece and again in modern times ensured medical progress

Our knowledge of the diseases of the ancients is derived from both their written records and material remains Although no direct reference to cancer is found prior to ancient Greek and Persian writings, archæological work in Egypt and Peru (Virchou, Ruffer, Elliot Smith, Herdlicka and Moodie) reveal the existence of osteomalacia, osteoporosis and osteosarcoma among other bone deformations

The Hebrew culture in its later arrival brought with it the mysticism of the East, the system of priestly castes and the arts and crafts of Egypt Its medical knowledge was founded upon Egyptian, Syrian and Babylonian influences [4] which were modified by Greek teaching and ultimately incorporated, together with beliefs and rules of social morality, into a single religious code [5] In Hebrew writings there are many instances where the symptoms given leave no room for doubt as to the presence of malignant growth [6] Thus (1) the case of King Jehoram, II Chronicles, xxi, 14 (Septuagint—Joram) may be identified as cancer of the rectum,[7] (2) the affliction, referred to in Numbers xiv 37, seems to deal with cancer of the tongue This may be compared with the case of Diocletian quoted by Cedrenus,[8] (3) some of the Talmudic descriptions of genital diseases correspond to cancer of the uterus,[9] and (4) the biblical description of bone diseases in Numbers, xxiv, 8, according to Rashi's commentary, provide symptoms which correspond to cancer of the bones [10] Again, the biblical injunctions and regulations regarding hygiene, sex-intercourse (Leviticus, xv, 25) and circumcision are obviously designed to prevent many sex diseases, including cancer

Prior to the time of Homer (*circa* B C 850) a mature culture had already grown up in Greece The Greek settlements, along the coast of Asia Minor and the neighbouring islands, with their pursuits of trade and war, brought them into contact with the Syrian, Persian, Mesopotamian and especially Egyptian cultures However, the adverse priestly influence was less felt in Greece Owing to the character of the people and local conditions some priests became actual protagonists of medicine, as in the case of the temple of Aesculapius at Epidaurus and that of Melampus at Argos Greek medicine found its origin in Egyptian teachings, such as those given in the temple of Seraphis at Memphis and elsewhere In course of time the study of medicine gradually drifted from the temples to independent philosophical schools where rhetoric, mathematics and arts were studied These schools spread from the Ionian islands to the mainland with Athens as its centre Here several generations of scholars laid a foundation to physiology and pathology, the practical aspect of which was approached in the light of the superficial humoral conception of that era Thus Pythagoras (B C 580-489) who travelled extensively in Asia Minor, Phœnicia and Egypt contributed considerably with his school to physiology and hygiene Alcmæon of Crotona, a disciple of Pythagoras, is credited with original work in anatomy and physiology and is believed to have been the first person to dissect for the sole purpose of learning anatomy Empedocles of Agrigentum (B C 504-443) and Democritus of Abdera (B C 494-404) contributed to physiology and anatomy During this period Democedes of Crotona, who was taken prisoner by the Persians, acted as physician to Darius and successfully treated his wife Atossa for a tumour of the breast Aristotle (B C 384-322) closely linked his general philosophy with the study of natural history and anatomy His work influenced later research on physiology and pathology

During this period cancer which was hitherto undifferentiated from benign tumours, ulcers and carbuncles, became recognised, named and studied in detail A treatment was developed based on excision and a variety of escharotics, including arsenical ointments A comprehensive collection of these medical studies is to be found in the *Corpus Hippocraticum* (Hippocrates of Cos, B C 460-377[11])

During its golden era, Greek learning followed in the wake of political and economic expansion It penetrated into Persia, reached the gates of India and returned to Egypt changed beyond recognition Under the Ptolomean dynasty, Alexandria, founded in B C 331 became a great cultural centre where Greek philosophy and medicine (Herophilus, Erasistratus) mingled with Hebrew theology Great improvements were made in surgery and special attention was given to gynæcology and obstetrics Thus, this outer perimeter of Greek culture, rather than its declining centre, became the source of inspiration With the rise of Rome, many of the Alexandrian physicians migrated to Italy, and to such strategic towns as Pergamus, Tralles, Miletus, Smyrna and Laodicea By B C 110 the argument between the Dogmatists and Empirics had resolved itself into a disagreement between the supporters of the methods of induction and deduction and most men sought the middle path between them

The writings on pathology of Cornelius Celsus (B C 25-50 A D) were the most accessible during the early Roman period Much of his description of malignant growth and its treatment can be traced to Hippocrates and his followers He identified the gross varieties of cancer and he excised breast cancer, advising against removal of the pectoralis major [12] Archigenes of Apamea, a contemporary of Celsus, perfected the operation of amputation, carried out hysterectomies, and operated upon mammary carcinoma [13]

Claudius Galen (131-203 A D) a native of Pergamus, Asia Minor, was educated in Alexandria, and migrated to Italy [14] He was the founder of experimental physiology and pathology, and made such a presentation of the humoral doctrine that his writings dominated medical thought for more than a thousand years According to this doctrine the body was regarded as containing four fluids—the blood from the heart, the phlegm from the head, the yellow bile from the liver and the black bile from the spleen Any adverse mixture of these fluids resulted in disease He considered that cancer developed from the concentration of black bile He noticed that tumours arose in the period following suppression of the menses, and with the appearance of hæmorrhoids These phenomena prevented the discharge of black bile, which became stagnant, resulting in cancer Leonidas of Alexandria (180 A D) broke away from Hippocratic conservatism He removed breast cancer extensively, cutting through healthy tissue with knife and cautery, and approached closely the modern technique of this operation

Social and political upheavals during the succeeding centuries led to stagnation in human learning Though familiar with the teaching of ancient Greece and Rome, the actual progress of Byzantine medicine was meagre Its important role was in preserving knowledge and passing it on to the Arabs Paul of Ægina (625-690) was one of the outstanding Byzantine physicians [15] The exile and dispersion of Hebrew culture (Titus, Hadrian) Roman and Byzantine decadence, and a religious fervour (diverted from high ideals of morality to persecution and devastation)—all brought learning to its lowest ebb during the succeeding centuries Intrigue and decay within the structure of the old civilisations contributed quite as much to the eclipse of knowledge (the Dark Ages) as did the incursions of Goths and Vandals across Europe and that of the Moslems from Asia through Africa into Spain

Through the centuries—long contact of the Arabs with Jewish communities in Arabia and later with the Jewish colleges in the Persian towns of Nehardea, Sora and Pumbaditha within the Eastern Caliphate, the Arabs became familiar with metaphysics, mathematics, astronomy and medicine [16] The Arabs were also influenced by Byzantine teaching through the Nestorian hospitals in Edessa (Mesopotamia) and Djondisapour (Persia) Within a few centuries, Bagdad, Cairo, and Cordova became renowned places of Arab learning The general contribution of the Arabs to medicine consisted largely in maintaining the Greek knowledge—only in materia medica and chemistry was an advance made

Rhazes (*circa* 900 A D), a famous surgeon of that period founded his teaching on that of the Greeks He made a significant remark, " when Galen and Aristotle agree, it is obvious that their opinion is correct, but when they disagree, judgment is indeed difficult " He produced the famous work which translated into Latin under the name of *Continens* served as the standard for mediæval therapeutics [17] According to Rhazes, carcinomatous growths were to be excised or completely burnt out, but if the tumour could not be completely extirpated, it was not to be incised In such cases the cautery alone was to be used Haly Abbas (*circa* 994) was a Persian physician who wrote *al-Kitab al-Maliki* the anatomical portion of which became for over a century the teaching text in anatomy at Salerno Albucasis (eleventh century) produced the *Compendium* which included the surgery of cancer Avenzoar-ibn-Zuhr (1092-1162) a late writer of the Western Caliphate, described gastric carcinoma of the œsophagus [18]

Whilst Islam spread throughout the east and south, Christianity (the ethical and ethnological amalgam of Greek and Hebrew cultures), progressed in the north and west Apart from the often cruel methods of expansion, it exercised an important educational and disciplinary role upon the newly converted tribes The religious and social work was centred in the monasteries Here, as conditions became more settled, the monks extended their learning to general science and medicine In Italy and later in France, contact was made anew with ancient Greek and Roman teachings mainly through Arabic writings These experiences of the Monte Cassino monastery led to the establishment of the medical school, " Civitas Hippocratica," at Salerno about the end of the tenth century The school came under the influence of contemporary Arabic teaching, and some of the teachers such as Constantinus Africanus (eleventh century) actually received their training in Bagdad At the medical school of Bologna (*circa* 1200) an approach was made to re-establish the methods of both Erasistratus and Herophilus in the study of human anatomy by dissection

During the thirteenth and fourteenth centuries, Italian medical schools made considerable progress under Taddeo Alderotti, Mondino de Luzzi and others and they became important seats of learning for many students from outside Italy From here medical training extended to the universities of Montpellier and Paris which were influenced by Jewish physicians from the Moorish colleges of Cordova, Granada and Toledo, and by Christian physicians from Salerno [19]

At the end of the fifteenth century the introduction of printing exerted a great influence on the spread of learning During the Renaissance period medical sciences progressed through the teaching of

Marc Antonio Della Torre and through the dissections and drawings by Leonardo da Vinci Paré (1510-1590) gave detailed descriptions of cancer, the transition from *cancer occultus* to *cancer apertus* His classification was still based on the ubiquitous black bile Harvey's discovery in 1619 of the circulation of the blood, facilitated the diagnosis and treatment of cancer, but added little to the etiology of the disease Nicholas Tulp (1593-1674) described various types of carcinoma He regarded mammary cancer as contagious

Andrew Vesalius (1514-1564) was one of the first to attack the theories of Galen Francesco Peccetti [20] gave a detailed study of surgical methods as applied to mammary cancer It was well known that mammary carcinoma rapidly finds its way to the axillary glands, and usually the entire breast was amputated as soon as evidence of a definite tumour presented itself Marcus Aurelius Severinus (1580-1656) described myxosarcoma, distinguished between benign and malignant tumours of the breast and extirpated the axillary lymph nodes

During this period Paracelsus opposed Galen's theory and claimed that cancer was caused by mineral salts in the blood This decline of Galen's authority and the distrust of his crude theories of etiology lead to a complete demoralisation in the treatment of cancer and encouraged the abuse of arsenic and other external and internal remedies It brought in its wake various fantastic theories and faith cures, ranging from spells to witches' brews The basic notion seemed to be that the uglier the disease, the nastier its remedy and that the mystery of the affliction must be countered by supernatural intervention In England anatomic teaching was not attempted until the latter part of the sixteenth century, when it was conducted by the barber-surgeons

The development of the microscope during the seventeenth century gave a great impetus to the study of anatomy and pathology With the discovery of the lymph-vessels (Owens 1652) came the lymph theory of the origin of cancer It is easy to understand this belief when we take into consideration the lymphatic spread of such tumours Helmont and others were now turning to chemical conceptions, and cancer was attributed usually to an excess of acid to be treated by alkalis

The role of chemical and mechanical irritants in producing and aggravating neoplasms, realised from earliest times, was strengthened by Pott's observation (1775) upon the prevalence of cancer among chimney sweeps During this period the general theory of irritability was applied to pathology (Haller, Fabre) Sauvages classified cancer among skin diseases [21]—a conception reminiscent of the earlier primitive ideas

The construction of the achromatic microscope in Paris in 1824 opened up a new era in cancer research In 1838 Schwann established the doctrine of cellular structure as a universal principle and discovered the nucleus and nucleolus of the cell In spite of very careful histological studies of tumour tissues all writers were led to believe in the blastoma origin of cancer This blastoma was assumed to develop, not from normal but from germ cells lying scattered between the tissue elements. Though burdened by this theory, the study of cancer had succeeded by 1860 in describing and classifying more accurately the main types of tumours, chiefly according to microscopic appearance.[22]

Correct conceptions of histogenesis were impossible, however, until Virchou[23] founded his cellular theory of pathology, according to which cells grew exclusively from other cells by endogenous reproduction. He failed, however, to interpret correctly the formation of cancer and believed that cancer cells arose from connective tissues.

Many authors attacked this theory but it was not until 1865, when Waldeyer traced the origin of cancer of stomach, liver and kidney to the epithelial cells of these organs, that the epithelial nature of carcinoma was generally accepted. During this period Recklinghausen and Koster established the group of endotheliomas. Recklinghausen in his work on neurofibromatosis and neural neoplasms attempted to link genetics with hereditary influences.

The tendency of carcinomatous metastases to occur elsewhere and at some distance apart led to the assumption that the systemic condition which had given rise to the original cancer produced another in a new location. However, it was soon observed that the metastatic foci were related to the original by virtue of lymph drainage. According to Billroth —"The carcinomatous and epithelial forms which are met with in primary carcinomata have always been found in the infection-tumours of the lymphatic glands. This appears to me to speak strongly in favour of the transportation of cell-elements, for it is scarcely conceivable that fluid from a columnar epithelial cancer should be capable of causing cells of the lymphatic glands to produce columnar epithelia. It is very probable that the epithelial gland-like prolongations not unfrequently grow into spaces between the bundles of connective tissue in which lymph circulates, for the tissue here offers the least resistance. I cannot ignore the fact, that by our more modern methods of operating (mammary cancer) where the skin is preserved as far as possible, so as to induce the wounds to unite quickly by first intention, recurrence seems to me to take place far more rapidly."[24] Koster's observations seem to confirm that the canal-like prolongations, mentioned by Billroth, are confined to the lymphatic vesssels, thus leading to the early infection of the lymphatic glands.

In 1877 Cohnheim advanced the theory that tumours arose not from normal cells, but mainly from isolated embryonal cells and tissue rests. This theory still holds good, but only for a few rarer tumours. The last decades of the nineteenth century were thus devoted to the detailed study of the morphology of tumours and the elucidation of their histogenesis. The introduction of aseptic surgery at this juncture led to the use of suppurative ligatures to remove inaccessible carcinomatous growth when the knife, cautery or corrosives were unsafe. Cancer research was concerned mainly with the study of fully developed tumour tissue. By the transplantation of such tissue, artificial metastases were formed and these again were studied.

Thus we see that the main trend of work was directed to the pathology rather than to its surgical and therapeutical nature Whilst the main objective in surgery was the complete removal of the growth, this was unattainable except in the case of superficial growths Realising the essential futility of surgical therapeusis, pathologists and surgeons directed their attention to medical treatment and prophylaxis Here again only defeat lay ahead, the more particularly since confusion between benign and malignant growths obscured any correct evaluation of the results

The beginning of the twentieth century marks the opening of the experimental era with the systematic study of tumours throughout the animal kingdom

Parasitic theories of malignant tumours were supported long ago by surgeons, such as Dupuytren, who believed in their infective nature According to Borrel, a cancer cell is a symbiosis between a cell and the virus which inhabits it , and he and Fibiger (1913) and others have made many interesting suggestions as to possible methods of access of the virus to the tissues by carriers, such as nematode worms in gastro-intestinal cancers, and the *acarus* and *demodex folliculorum* in cancers of the skin (also in nipple and duct cancers of the breast) The fact that a long series of supposed specific bacterial infections, of fungi, yeasts and protozoal organisms have been shown not to be causal, hardly supports the infective theory of cancer A further difficulty in accepting this theory has been the " specificity " of many tumours when inoculated experimentally, which would suggest a specific strain for each type of tumour Less specificity, however, has been found by a number of workers on fowl tumours and fowl leukæmia, and some have suggested that one agent may produce in different animals, carcinoma, sarcoma, endothelioma, or myeloid or lymphatic leukæmia The modern infective or virus-theory has received great support from Gye's researches, and from those of Peyton Rous and of Shope (on three experimental sarcomas, and the papilloma of " cottontail " rabbits), of McIntosh (on Rous sarcoma and tar-induced fowl tumours) and of Andrewes (on Shope fibroma and tar-stimulation, and on virus antibodies and the " latency " of virus infections) " Some who would be willing to support an infective theory for cancers of the skin, upper air-passages, gastro-intestinal tract and cervix (all accessible areas and open to exogenous infection) would consider cancers of the internal organs as more likely to be due to endogenous viruses, similar in nature to enzymes or catalysts, and arising as autogenous products of some disorder of metabolism Of interest is the theory that the cancer cell is atavistic, returning towards the primitive embryonic type of cell, with its almost indefinite growth capacity (Blair-Bell and others) There is also the theory, difficult to prove or disprove, that the cancer cell is an aberrant or anarchic type of cell, with a nuclear disease, possibly due to a gene-mutation (Lochart-Mummery) " (J Douglas Webster—*The Periodicity and cause of Cancer*, London, 1940)

In connection with breast cancer the recent evidence as to a transmissible milk factor bridges the difference between mammalian and avian cancer and incidentally seems to undermine the whole virus theory of malignant growth The fact that mammary excretions are brought into being and are controlled by pituitary and sex hormones, which in themselves are capable of functioning as chemical carcinogens, hardly supports a virus theory of the carcinogenic milk factor The presence of nucleoproteins or nucleic acid in the active milk agent [25] does not necessarily vindicate the virus hypothesis It is much more in agreement with the modern assumption of associations between the chemical carcinogen and enzymic complexes in all types of malignant growth Especially in the case of mammary tumours the virulent factor may acquire organic complexity and mobility, that is, become transmissible through the association of a chronic excess of steroid carcinogen or hormone with the embryonic cells or tissue rests In any event, in view of recent studies of the chemistry of viruses and the function of optically active chemical complexes it would appear that the virus and chemical conceptions of cancer are not so utterly divergent from one another They merely represent the biologist's and the chemist's points of view of one and the same set of conditions, where the simplest form of organised matter becomes synonymous with the more omplex optically active chemical unit Tumour-transmission through mmary gland excretions demonstrates the possibilities of the earlier ypotheses as regards the spread of cancer along the lymphatic canals

In 1915 Yamagiwa, echoing the earlier observations of Pott, demonstrated the cancer-causing properties of coal tar Later work on the action of wood tar, barley bristle and other irritants on rats, revived the old irritation theory of tumours The mechanical aspect of this problem was, however, soon overshadowed by the isolation of specific chemical carcinogens from various tarry pyrolytic products and later, by the synthesis of an ever-increasing number of carcinogenic unsaturated hydrocarbons (Butenaudt, Kennaway, Dodds, Cooke, Fieser *et al*)

The close constitutional link between the synthetic carcinogens and many steroid metabolites, capable in themselves of causing malignant growth, provides a common metabolic ground for synthetic and spontaneous cancer The further extension of synthetic carcinogens to mustard oils and certain azo-dyes seems to link these substances with the steroid forms as possessing in common a reactive point K, a region of high electron density, at which the association with enzymic complexes takes place [26] The fact that such inductive agents as radium emanations, X-rays and other radiations may induce metabolic distortions characterising cancer, widens still further the range of carcinogenic influences

The work of Warburg, Hopkins and others on suppressed enzymic activity in relation to malignant growth, especially glycolysis and the equilibrium of SH SH -SS, constitutes an important contribution to the etiology of cancer Again, the transition of steroid hormones into the essential cell constituent—cholesterol, as well as chromosomal changes and gene mutation induced by various carcinogens, connects the resulting functional and structural changes and throws much light upon the genetic aspect of carcinogenic action as related to the somatic cell

The present trend in research seems to converge on the etiology of cancer and the elaboration of corrective, and, better still, preventive measures [27]

In summing up, we find that in medicine as in other spheres of human activity there is a certain continuity or gradual development Thus, modern osteology may be traced back to the symbolic bones of the Hindus, the Talmudic " Luz "—the magic bone of resurrection—and beyond that the miraculous scapula of the Far East In the case of cancer, the modern aseptic surgery and the radium and X-ray treatment of tumours must be viewed as direct descendants of the antique cautery, the knife and the escharotics The present contact and inductive carcinogens and the virus theory find their inception in the earlier assumptions on cancer-causing irritants and parasites The modern transmissible milk factor of breast cancer is not too remote from Tulp's conception of mammary cancer as being contagious (seventeenth century)

The mediæval stress upon mineral salts or acidity as a significant factor in the etiology of cancer is not strange to the modern investigator who seeks to establish the relationship of the geographical distribution of human cancer to the type of soil, the mineral components of cancerous to those of normal tissue, and ratio of K—Na to Ca, K to Na and those of K isotopes

Again, Hippocrates and Galen's humoral black bile theory is not utterly absurd to one who regards the protracted distortion of steroid hormonal equilibria as an important carcinogenic condition

REFERENCES AND NOTES

[1] The Emperor Shen Nung (2735 B C) is usually referred to by legend as the " father of Chinese materia medica " and was supposedly the author of an Herbal which is now represented by a 40 volume work called the " *Pen Ts'as* " or " *Pun Tsao* "

[2] About 500 B C the newly evolved contributions of Greek thought began to filter eastwards Not only Persia but India and even China were influenced by this diffusion which followed the slow-moving, transcontinental, commercial routes of the ancient world While it is possible to discover traces of primitive medicine in Hindu literature, prior to the First Christian Century, the first evidence of what might be termed a system of medicine is traceable to a later date (Charaka second century A D , Suscruta between sixth century B C , and fifth century A D , Vagbhata *circa* A D 625)

[3] The knowledge of Taaut, engraved upon the columns and collected in papyri entitled *Embre* or *Scientia Causalitalis* which served as a medical code for the Egyptians, according to Diodorus Edwin Smith Papyrus written seventeenth century B C as a copy of an earlier work composed *circa* 2500 B C available in a modern reprint and English translation by J H Breasted—*The Edwin Smith Surgical Papyrus* (1930), Chicago *Papyrus Ebers* (*circa* 1550 B C) on Pharmacology, C P Bryan (1930), London

[4] The earlier medical records are found in the Pentateuch, the first four books of which are considered synchronous with the *Iliad*—850 B C ending about 150 B C

[5] The Talmud (specifically the Mishnah plus Gemarah) a work occurring in two issues—*The Jerusalem Talmud* (fourth century A D) and the *Babylonian Talmud* (fifth century A D)

[6] PREUSS, JULIUS (1923), *Biblisch—Talmudische Medizin* Berlin

[7] BARTHOLINUS, THOMAS (1672), *De morbis biblicis* Frankfort

[8] BOCHART (1675), *Hierozoic*, ii, col 620

[9] T NIDD, VIII, 2 Nidd 66a Tetrabibl IV sermo 4, c 108 (R Shimeon Ben Gamliel)

[10] BRIM, CHARLES J (1936), *Medicine in the Bible*, The Pentateuch—Torah New York

[11] ADAMS, FRANCIS (1849), *The Genuine Works of Hippocrates* London

[12] SPENCER, W G (1935-38), *Celsus* , *De Medicina*, 3 vols , 3, 592 Cambridge

[13] BRUNN, WALTER VON (1928), *Kurze Geschichte der Chirurgie*, p 91 Berlin

[14] WALSH, J (1935), " Galen's Writings and Influences Inspiring Them," III *Ann M Hist* , N S , 7, 428

[15] AEGINA, PAUL OF (1528), *Pauli Aeginetae de re medica libri septem graece* Venice

[16] The Arab tolerance towards Jews and the encouragement given to their scholarship and crafts made the Jewish contribution an integral part of Arab culture, and Judeo-Arabic would be a more accurate assessment of that culture Apart from the great theological scholars, the *Gaonim* of Babylonia, the culture of the dispersed Jews of that period, is represented by Philo, the philosopher of Alexandria 40 B C , Samuel, the astronomer of Nehardea *circa* third century A D , Zedekiah, physician ninth century, Solomon ibn Gabirol, poet and philosopher eleventh century, Rashi, theologian eleventh century, Jehudah Halevi, physician and poet eleventh to twelfth centuries, Abraham ibn Ezra, theologian eleventh to twelfth centuries, Rabbi Benjamin of Tudela, traveller and geographer twelfth century, and Moses ben Maimon (Maimonides) physician and philosopher twelfth century

[17] RHAZES (1510), *Ad Almansorem libri decem* Venice

[18] LONG, E R (1928), *History of Pathology* Baltimore

[19] Henri de Mondeville (*circa* 1260-1320), professor of anatomy, surgery and medicine at Montpellier Guy de Chauliac—followed his predecessor Mondeville in regarding anatomy as the proper foundation for surgery *Chirugiae tractatus septem cum antidotario* (written 1363, published in Venice 1470)

[20] PECCETTI, FRANCESCO (1616), *Opera chirurgica* Florence

[21] SAUVAGES (1759), *Pathologia methodica sêu de cognoscendis morbis* Lyons

[22] MARJOLIN, JEAN NICHOLAS (1837), *Coeurs de pathologie chirurgicale professé a la Faculté de Medicine* Paris

MULLER, JOHANNES (1838), *Ueber den feinern Bau und die Formen der Krankhaften Geschwülste* Berlin

VELPEAU (1853), *Trâite des maladies du sein, et de la region mammaire* Paris

[23] VIRCHOU (1858), *Die Cellularpathologie in ihrer Begrundung auf physiologische und pathologische Gewebelehre* Berlin

[24] METTLER, C (1947), *History of Medicine* Philadelphia

[25] GRAFF, S , MOORE, D H , WENDELL, M S , RANDALL, H T , and HAAGENSEN, C D (1949), *Cancer*, 2 (5), 755

[26] FIESER, L F (1941), *Univ of Pennsylvania, Bicentennial Conference* Philadelphia

BERENBLUM, J , and SCHOENTAL, R (1946), *Cancer Res* , 6, 703

COPISAROW, M (1948), *Edin Med Journ* , 55, 754

[27] COPISAROW, M (1939), *Edin Med Journ* , 46, 781 , (1942), 49, 425

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Modern Trends in Neurology Edited by ANTONY FEILING, B A, M D, F R C P Pp ix+717, with 202 illustrations London Butterworth 1951 Price 63s

Contributions from more than 20 authorities in this country and the United States have been brought together in this book to form an up-to date account of some of the subjects in neurology in which valuable advances have been made in recent years

The editor stresses the point that his selection of material has been based on the progress which has been made in the different aspects of neurology, and though such selection has necessarily been a limiting factor to the completeness of the work, the scope of the book as it appears is immense

All the contributors are of a very high standard, but Denny Brown's chapter on the Frontal Lobes and their functions is quite outstanding It is the longest chapter in the book and gives a very complete account of present-day work, together with all the ideas and experiments which have gone before The chapter on Intracranial Tumours by Northfield and Russell and Intracranial Aneurysms by Meadows likewise deserve special mention for their interest and detail

Bull's chapter on Diagnostic Neuro-radiology is a very welcome inclusion with its fine illustrations

These, with all the other excellent sections in the book, packed with valuable information, make it an essential part of the equipment of every neurologist

Primary Carcinoma of the Liver By CHARLES BERMAN, M D, B CH Pp xvi+164, with 83 illustrations London H K Lewis 1951 Price 35s net

This is an interesting monograph on what might be called geographical pathology, as it is primarily a study of malignant disease of the liver as it occurs in the Bantu race of Africa The author shows how this disease is the most common form of malignancy amongst this people, and discusses the question of genetic as against environmental causes He finds that cirrhosis of the liver is also a common feature amongst this race, and that is related to food conditions which in many cases are highly defective Hæmatochromatosis also seems to be frequent in South Africa He also draws attention to a similar frequency of this disease amongst races in the Indo China region With regard to the disease itself he recognises certain groups mainly on their clinical features

The book is well illustrated and furnished with an extensive bibliography As Sir Ernest Kennaway mentions in his Foreword, a work of this nature should stimulate similar observations amongst other races We might in that way get useful information as to environmental factors in the cause of cancer

The Rational Treatment of Catarrh By W ANNANDALE TROUP, M C, M D, CH B Pp 85, with 8 illustrations London Chaterson Ltd 1951 10s 6d

This book deals with the treatment of nasal catarrh and sinusitis with infra-red and the intranasal application of ultra-violet light by a Kromayer Mercury Vapour Lamp Special applicators are shown for both nasal cavities and nasopharynx

The physiological effect of this treatment is indicated, but it is based upon theoretical rather than clinical experience

This form of therapy is associated more with tubercular infection of the nose than suppurative sinusitis—in the latter condition favourable results have rarely been obtained

Heart Disease Its Diagnosis and Treatment By EMMANUEL GOLDBERGER Pp 651, *with* 90 *illustrations London Henry Kimpton* 1951 *Price* 70s

The publication of a textbook on Heart Disease by an eminent cardiologist is almost a quarterly event The most recent addition by an author who is better known on this side of the Atlantic for his pioneer work on unipolar lead electrocardiography, follows the accepted pattern for such books

The preface consists mainly of an apologetic admission that most cases of cardiovascular disease can still be diagnosed by the clinician without any of the modern ancillary tests such an admission thereby justifies the material to follow, although mechanical tests are in no way neglected An orderly succinct somewhat dogmatic presentation of all aspects of cardiology follows, the whole of which is very readable

Criticism might be expressed that only five pages are devoted to functional disorders of the heart The treatment of this latter condition by the Freudian concept of " transference " is not acceptable to most physicians, also, is pregnancy to be discouraged " if mitral stenosis is present ? "

Graduates seeking guidance on cardiac disorders common or rare, will find this book of value

Growth and Development of Children By E H WATSON, M D , and G H LOWREY, M D Pp 260, with 54 illustrations Chicago Year Book Publishers 1951 Price $5 75

The welcome emphasis now being placed on the study and promotion of optimal health in childhood is being reflected by the publication of an increasing number of books on various aspects of growth and development This book is a product of the Pædiatric Department of Ann Arbor It is a general survey of growth and development from conception to maturity and is intended for students, post-graduates and practitioners, rather than research workers Emanating from a leading pædiatric centre, under the ægis of Professor James L Wilson, it can be strongly recommended as a simple, practical portrayal of the subject, and it contains an extensive bibliography for those who wish more detailed information

The Medical Annual 1951 Edited by Sir HENRY TIDY and A RENDLE SHORT Bristol John Wright 1951 Price 27s 6d

The 69th edition of the *Medical Annual* follows the usual lines Articles of importance in every field of medicine are abstracted, but special attention is given to those of outstanding importance such as the chronic rheumatic disorders, anticoagulants and chest surgery The section of Legal Decisions is of special interest One curious finding that is fully discussed is that the change of control of hospitals does not constitute legal " nationalisation "

The book is very fully illustrated by plates, many of which are in colour The present edition of the *Medical Annual* amply fulfils the purpose for which it is intended

Between Life and Death By HARLEY WILLIAMS, M D , D P H Pp 288 London Jonathan Cape 1951 Price 15s net

This is a third series of biographies by an author who has already made a name for himself in *Doctors Differ* and *The Healing Touch* The biographies are mostly medical but include one or two whose contact with medicine is indirect The series of portraits include John Hunter, J Y Simpson, Pasteur, Lister, Freud, Barnardo, Truby King and Banting, also the originators of ether anæsthesia, Mrs Eddy, Margaret McMillan and Ehrlich These pictures are sympathetically drawn and beautifully written Dr Harley Williams has proved himself a master of this type of record, and this new series will be welcomed by the medical profession

The Treatment of Varicose Veins By S M RIVLIN Pp viii+56, with 5 plates and 25 figs London William Heinemann 1951 Price 10s 6d net

This is a concise monograph with an essentially practical outlook A useful classification is illustrated in Figs 1-10 Well-established lines of treatment are described Ligation is advocated in all cases where there is a retrograde flow of blood within the vein, and the elastoplast bandage is recommended for varicose ulcer

Alice and the Stork By EGBERT MORLAND Pp 87, illustrated London Hodder & Stoughton 1951 Price 7s 6d net

This is the life story of Alice Gregory who was one of the creators of the training school for midwives at Woolwich It is compiled from the data of Miss Maud Cashmore who was another of the pioneers The story also includes the struggle to raise the status of the midwife—an interesting tale

The Isocortex of Man By P BAILEY and G VON BONIN Pp xi+301, fully illustrated Urbana Univ of Illinois Press 1951 Price $5 paper, $6 cloth

This is an important study of the human brain The authors have summarised the history of the subject and have a wide experience of the brains of the primates They describe the superficial sutures of the brain and the details of serial sections of different parts Considerable attention is given to the various cortical areas, intercortical connections, afferent and efferent connections and to the functional significance of various parts The last chapter is devoted to the functional significance of the anatomic and histological findings A large bibliography is included

This authoritative work is likely to become a classic

The Story of St Luke's Hospital—1750 1948 by C N FRENCH, C M G, C B E Pp 212 London Heinemann 1951 Price 8s 6d net

In 1950 six gentlemen of the City of London met to discuss a project for establishing a hospital for the care of poor lunatics The result was the founding of one of the earliest of the voluntary hospitals The book goes on to describe the progress of the hospital and the improvement in the lot of the insane It is full of detail and accounts of the state of affairs at various stages The old hospital closed in 1916 and some years later the management undertook to provide for functional and organic nervous disorders at Woodside Well written and interesting, this is a record of medical progress

Wonderfully Made By A RENDLE SHORT, M D, F R C S Pp 159, illustrated London Paternoster Press 1951 Price 6s net

Professor Rendle Short has written a short book for the layman on the human body and some modern discoveries about its structure and functions He touches on several systems of the body, gives an account of vision and hearing, and the development of the embryo, and there is a long chapter on the problem of Man's origin The book is one which should appeal to the intelligent layman

The Essentials of Modern Surgery Fourth Edition, edited by R M HANDFIELD-JONES, M C, M S, F R C S, and Sir ARTHUR E PORRITT, K C M G, C B E, M A, M CH, F R C S Pp xv+1263, with 641 illustrations Edinburgh E & S Livingstone 1951 Price 55s net

The fourth edition of this well known textbook has been revised and brought up to date after an interval of twelve years, and although new chapters have been added, particularly on antibiotics, the book has not increased in size Random sampling indicates that the volume has retained its reliability as a source of information to students, to whom it may be confidently recommended Perhaps in the next edition further improvement in the illustrations will be possible, particularly in some of the photographs

Surgery of the Stomach and Duodenum By CLAUDE E WELCH Pp 349, with 79 illustrations Chicago The Year Book Publishers 1951 Price 65s net

This is the first of a series of " Handbooks of Operative Surgery " the professed object of which is " to present simply but vividly the step by step technic of the more common surgical operations " This volume is a successful and promising start

The author is a surgeon in the Massachusetts General Hospital and his preferences reflect the practice in that hospital, but there is no undue emphasis on personal opinions and the important alternative techniques are well described Sections on pre- and post-operative care are included, and the whole is well balanced The text is concise and practical but fundamental principles are never forgotten or obscured by the detail The 79 full-page plates represent more than 450 excellent line drawings, each illustrating a stage of the technique described on the opposite page

This book will be welcomed by surgeons in training, but it is by no means elementary and can be warmly recommended to more experienced surgeons

The Postnatal Development of the Human Cerebral Cortex Vol IV The Cortex of the Six-Month Infant By J LEROY CONEL Pp viii+191, with 7 tables and 108 full plates Harvard University Press (London Geoffrey Cumberlege) 1951 Price 82s 6d net

The fourth volume of this important work is concerned with the cerebral cortex of the six-month-old child as demonstrated by cresyl violet, Cajal, Cox-Golgi and Weigert methods of staining The format is the same as in the three previous volumes, which described the brains of newborn, one-month and three-month-old children

An effort is made to reduce the main features of each cortical region to mathematical terms by measurement of laminar thickness together with enumeration and calibration of the cells and fibres in every layer It is doubtful whether measurements to the third decimal place in millimetres have any significance for such indefinite structures as the cortical laminæ, and unfortunate that many of the photomicrographs fail to demonstrate the features for which they are intended

The use of multiple staining methods in the study of the cerebral cortex is to be welcomed, though the evaluation of the results must depend on the degree of variation found in brains of the same age, a feature which receives scant attention

This volume is produced in excellent style and as an integral part of a larger series it has a special importance

Surgical Forum—American College of Surgeons Pp 665 London W B Saunders 1951 Price 50s net

This volume represents the papers presented at the Surgical Forum of the Clinical Congress of the American College of Surgeons, 1950 The forum provides an opportunity for young research workers to bring their experiments before the notice of those attending the meetings of the College, and the reviewer can testify to the outstanding success of the arrangement It is natural that the papers, which cover the whole field of surgery, are not all of a high standard, but it is important that the young workers be given an opportunity of communicating their views , and now the American College of Surgeons has published the short papers and abstracts of the longer ones Naturally such an accumulation of information on many different subjects does not lend itself to review, but the American College is to be congratulated first on the introduction of the surgical forum and secondly on making it readily available in this form to surgeons throughout the world

The Nature of Disease Institute By G E R MCDONAGH, F R C S Pp lviii+457 London Heinemann 1951 Price 21s net

The author remarks that he is compelled to publish in this form because the weekly journals are closed to him The material is thoroughly unorthodox

NEW EDITIONS

Surgical Nursing and After-Treatment. By M. C. RUTHERFORD DARLING, M.D., M.S., F.R.C.S., and T. E. WILSON, M.D., M.S., M.SC., F.R.C.S., F.R.C.S.E. Tenth Edition. Pp. ix+630, illustrated with 188 figures. London: J. & A. Churchill. 1951. Price 6s.

This popular and successful textbook which has held the field for over thirty years has been brought thoroughly up to date. It contains a great deal of useful information in an attractive form, everything in fact which the surgical nurse requires to know. The present edition maintains the standard of its predecessors and can be strongly recommended.

The Pharmacology and Therapeutics of the Materia Medica. By WALTER J. DILLING, M.B., CH.B., M.P.S. Nineteenth Edition. Pp. xxxii+598. London: Cassell & Company. 1951. Price 21s. net.

This volume, like its predecessor, provides both students and practitioners with the recent views on the pharmacological actions, modes of administration and relative therapeutic merits of modern drugs. This nineteenth edition has been thoroughly revised to conform with the official preparations of the *British Pharmacopœia of* 1948. It can be well recommended.

Black's Medical Dictionary. By J. D. COMRIE and W. A. R. THOMSON. Twentieth Edition. Pp. x+1013, with 417 figures and 16 plates. London: A. & C. Black. 1951. Price 30s. net.

The first edition of this popular book appeared in 1906 under the editorship of the late Dr J. D. Comrie, and since then over 150,000 copies have been issued. The present edition has been very extensively re-written and reset and many of the illustrations have been changed. The general arrangement and plan of the work remains the same. As a reference book it aims to occupy a position between a technical dictionary and a guide to the lay treatment of the commoner ailments. This useful work seems likely to continue its well deserved popularity.

The Early Diagnosis of the Acute Abdomen. By ZACHARY COPE, B.A., M.D., M.S., F.R.C.S. Tenth Edition. Pp. xv+270, with 39 illustrations. London: Oxford University Press. 1951. Price 15s. net.

There is no essential change in the latest edition of this now famous little book apart from slight alterations in the text and the addition of one new radiograph. As before, this book endeavours to help in the diagnosis of one of the most difficult and sinister conditions in medicine—the acute abdomen.

A Pathology of the Eye. By EUGENE WOLFF. Third Edition, edited by EUGENE WOLFF. Pp. 364, with 318 illustrations. London: H. K. Lewis Ltd. 1951. Price 55s. net.

Eugene Wolff's *A Pathology of the Eye* has for long been the foremost English work on general ocular disease. The third edition maintains the standard of its predecessors. The excellent illustrations have always been a prominent feature and these have been increased to the extent of one hundred. The subject-matter has been brought up to date and questions of recent interest discussed with the author's customary conciseness. His opinions, as on Retro lental Fibroplasia, are dogmatic, but this is a virtue in a book which "is intended as an introduction to a subject whose essentials most Students and Ophthalmic Surgeons find it difficult to come by."

Medical Disorders of the Locomotor System By E Fletcher Second Edition Pp xii+884, with 337 illustrations Edinburgh E & S Livingstone 1951 Price 60s net

Interest in the rheumatoid diseases has been stimulated by the discovery of the action of cortisone and A C T H and the recent advances in our knowledge arising from this discovery have been incorporated in the new edition of this book In addition to a chapter on Cortisone and A C T H new sections have been added on pain, physiology and pathology of bone, synovial fluid, synovial mucin, psychiatric aspects of locomotor disorders and hydrotherapy The second edition maintains the high standard set in the first edition published in 1947

BOOKS RECEIVED

Bowley, Agatha H , ph d Child Care (*E & S Livingstone Ltd , Edinburgh*)	10s 6d net.
Braasch, William F , m d , and Emmett, John L , m d Clinical Urography An Atlas and Textbook of Roentgenologic Diagnosis (*W B Saunders Company, London*)	£6, 5s
Bull, H Cecil H , m a , m b , m r c p X-ray Interpretation Second Edition (*Oxford University Press, London*)	25s net
Burrows, H Jackson, m d , f r c s , f r a c s Treatment by Manipulation Second Edition, Fully Revised (*Eyre & Spottiswoode, London*)	12s 6d net
Central Council for the Care of Cripples Summary of Legislation and Directory of Organisations for the Care of the Physically Handicapped (*William Heinemann (Medical Books) Ltd , London*)	5s 6d net
Fellowship Examination Papers for the Diplomas of the Royal College of Surgeons, Edinburgh 1947-51 (*E & S Livingstone Ltd , Edinburgh*)	5s 6d net
Fulton, John F , m d Decompression Sickness (*W B Saunders Company, London*)	42s 6d
Hubbard, L Ron Dianetics The Modern Science of Mental Health (*Derricke Ridgway, London*)	30s net
Kroger, William S , m d , and Freed, S Charles, m d Psychosamatic Gynecology (*W B Saunders Company, London*)	40s
Martin Doyle, J L C , m r c s (eng), f r c p (lon), d o (oxon) A Synopsis of Ophthalmology (*John Wright & Sons Ltd , Bristol*)	20s
Moloy, Howard C , m d , m sc Evaluation of the Pelvis in Obstetrics (*W B Saunders Company, London*)	12s 6d
Monro, Thomas Kirkpatrick, m a , m d , ll d The Physician As Man of Letters, Science and Action Second Edition (*E & S Livingstone Ltd , Edinburgh*)	21s net
Moore, Robert Allan A Textbook of Pathology Second Edition (*W B Saunders Company, London*)	63s
Murray, J Barrie, m a , m d (cantab), m r c p Some Common Psycho somatic Manifestations Second Edition (*Oxford University Press, London*)	17s 6d net
Ogilvie, Robertson F , m d , d sc , f r c p ed , f r s e Pathological Histology Fourth Edition (*E & S Livingstone Ltd , Edinburgh*)	40s net
Edited by Sandweiss, David J , m d , f a c p Peptic Ulcer (*W B Saunders Company, London*)	75s
Thomson, A P , m c , m d , ch b (birm), f r c s (lon), Lowe, C R , m d , ch b (birm), m r c s (eng), l r c p (lon), d p h , and McKeown, Thomas, b a (b c), ph d (mcgill), d phil (oxon), m d (birm), m b , b s (lon) The Care of the Ageing and Chronic Sick (*E & S Livingstone Ltd , Edinburgh*)	7s 6d net
Town, Arno E , m d Ophthalmology (*Henry Kimpton, London*)	70s net
Whiting, Maurice H , o b e , m a , m b , b ch (cantab), f r c s Ophthalmic Nursing Sixth Edition (*J & A Churchill Ltd , London*)	8s 6d net

Edinburgh Medical Journal

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ON OCCLUSION OF THE ABDOMINAL AORTA

By CATHERINE C BURT, B Sc, M B, Ch B, Sir JAMES LEARMONTH, K C V O, C B E, Ch M, F R C S E, and R L RICHARDS, M D, M R C P E

(*From the Department of Surgery, University of Edinburgh*)

PART I—INTRODUCTION

Historical Aspects—In 1814 Robert Graham of Glasgow reported a "case of obstructed aorta" The case which he described was undoubtedly one of coarctation, but in the discussion he mentioned a museum specimen which belonged to Mr Allan Burns in which "the aorta is plugged up by a laminated coagulum, just above the bifurcation of the iliacs, into both of which this substance extends" This has been accepted by most authorities as the first mention of occlusion of the aortic bifurcation, but the condition was certainly recognised at an earlier date and had been described by, among others, Severinus (1632) and Fantonus (1679) In 1818, at a meeting of the Faculty of Medicine in Paris, Goodisson of Dublin reported a case of obliteration of the lower part of the aorta associated with calcification Details of the case are not given, but it is presumably that which he described in the Dublin Hospital Reports of the same year His observations were made on a female anatomical subject, the clinical history was not available The aorta was found to be obstructed from the origin of the inferior mesenteric artery to the bifurcation, the occluding mass extended into the iliac arteries, on the left as far as the bifurcation of the common iliac and on the right for half the length of the common iliac The wall of the occluded portion of the aorta is described as "like a sheath of bone" The obstruction was of long standing, and the mammary, lower intercostal, ovarian, lumbar and circumflex iliac arteries were enlarged and tortuous The intestines and abdominal viscera were healthy and the lower limbs were described as normal (Goodisson, 1818a and b) According to Hesse (1921), Allibert (1828) described aortic embolism in 2 children aged 3 and 3½ years respectively the first well-documented case of occlusion of the aortic bifurcation, however, is that reported by Barth (1835) The patient was a woman of 51 with an enlarged heart and an irregular pulse, who had had repeated attacks of hæmoptysis Swelling appeared and pain was felt first in the right lower limb and some months later in the left At autopsy mitral stenosis was found , below the origins of the renal arteries the aorta was obstructed by a clot which extended into both iliac arteries and into their branches Barth's paper contained a detailed consideration of the pathological nature of the occlusion and of the anatomy of the collateral circulation to the lower limbs

During the latter half of the nineteenth century a number of further cases were reported, and in 1898 Welch was able to find 59 cases of occlusion of the abdominal aorta by embolism or thrombosis By 1921 Hesse could collect 72 cases Since then the number of published cases has increased greatly and no useful purpose would be served by an attempt to review them

In the majority of the reports up to and including that of Hesse, cases of embolism and thrombosis were considered together because in many cases it was difficult to decide which of these two processes was primarily responsible for the occlusion In 1911 Labey performed the first successful embolectomy, and two years later Bauer (1913) removed an embolus from the aortic bifurcation and thereby restored the circulation to the lower limbs It then became important to distinguish between embolism and thrombosis, and this is reflected in the papers which have been published since that time , most deal with either embolism or thrombosis

Albright and Leonard (1950) have recently reviewed the literature on embolism of the abdominal aorta Their material consists of 193 reported cases of which 26 were successfully treated by embolectomy, but their list of cases certainly does not include all the published cases of embolism and probably includes some cases of thrombosis The number of published cases of thrombosis of the abdominal aorta does not give a true indication of its incidence Until Leriche (1940, 1946) drew attention to the fact that thrombosis of the aortic bifurcation can occur insidiously and may produce only mild symptoms referable to the lower limbs and to sexual function in the male, it had always been assumed that the condition was associated with a dramatic onset similar to that observed in cases of embolism, and that it was almost invariably fatal Within recent years improved surgical technique and the availability of potent anticoagulant drugs have tended to focus attention upon the treatment of cases of embolism and thrombosis, and the events which follow the lodgement of an embolus or the development of an intra-arterial thrombus have been somewhat neglected There may be some justification for this attitude for it is difficult to add anything to the description given by Welch (1910) in his masterly article Nevertheless our knowledge of vascular physiology is considerably greater than it was forty years ago, and we believe that the time is opportune for a reconsideration of the clinical features which follow occlusion of the abdominal aorta As an introduction to our clinical observations we shall consider certain anatomical, physiological and pathological aspects of the problem

Anatomical Aspects—Normally the abdominal aorta extends from the aortic opening in the diaphragm opposite the twelfth thoracic vertebra, to the fourth lumbar vertebra It is formed by fusion of the two primitive dorsal aortæ, its length in any particular subject depending upon the extent to which fusion of these two primitive arteries has taken place Thus its division into the two common iliac arteries may be delayed to the level of the fifth lumbar vertebra, or may occur as high as the second lumbar vertebra Sometimes the primitive dorsal aortæ fail to fuse, and " double aorta " is present, sometimes the adjacent walls of the primitive dorsal aortæ are not absorbed, and a more or less complete septum persists throughout the length of the vessel (Fig 1) It is odd that neither of these rare anomalies leading to narrowing has been recorded in association with pathological blocking Normally also the aorta narrows rather suddenly after it has discharged its important abdominal duty of giving off the cœliac and superior mesenteric arteries, but that is a level where the rapid arterial blood flow tends to prevent the lodgement of an embolus or the growth of a thrombus Rarely a congenital narrowing of the abdominal aorta is present (Maycock, 1937) One other developmental anomaly is of clinical importance Sometimes the bifurcation of the abdominal aorta consists of one common iliac artery and one internal iliac artery, the

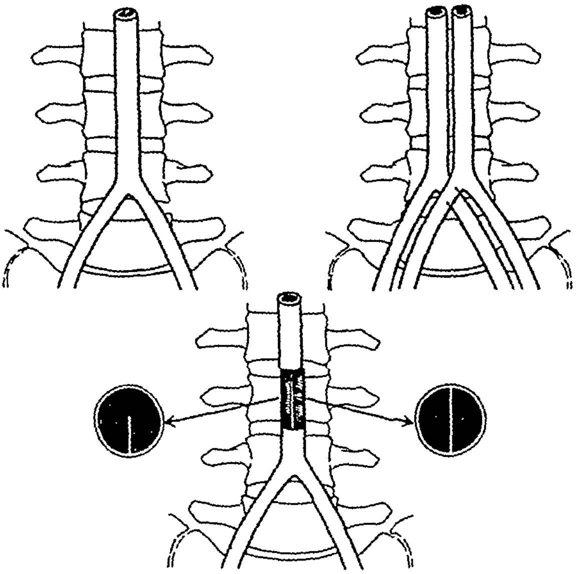

FIG 1 —Upper left normal anatomy of abdominal aorta Upper right reduplication of abdominal aorta and its bifurcation Below possible sub divisions of single abdominal aorta

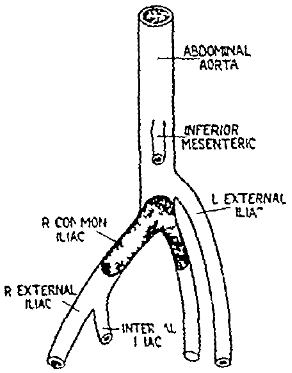

FIG 2 —Abnormal aortic bifurcation into common and internal iliac arteries

external iliac artery on the abnormal side arising from the aorta at a higher level When such a bifurcation is obstructed, it is possible for the circulation of one lower limb to be preserved (Fig 2)

Physiological Aspects —The function of the abdominal aorta is to nourish the viscera and the lower limbs It is said that the abdominal aorta—or at least its lowest segment—may rapidly diminish in calibre as a result of arterial spasm We have never seen the aorta of an adult react to handling or to incision in this way, and we doubt if its wall contains a sufficient proportion of muscle fibres to make it possible The clinical evidence for aortic spasm is the occasional occurrence of transient complete paralysis of both legs in patients suffering from thrombo-angiitis obliterans and in certain cases of pseudo-embolism to which we shall refer, but this is probably due to spasm of the common, external and internal iliac arteries which have more muscular walls

Pathological Aspects —For practical purposes occlusion of the aortic bifurcation may be due to thrombosis, to embolism or to a combination of these two processes Thrombosis occurs secondary to disease of the vessel wall , like any other artery the aorta may be the site of atheroma That thrombosis does not occur more frequently on an atheromatous aortic ulcer is due to the rapid rush of blood over it, and it is understandable that blocking of the aorta by thrombus as a rule begins in the common iliac arteries, the calibre of which is smaller than that of the aorta, and extends proximally up to and even higher than the bifurcation Less commonly, occlusion of the abdominal aorta may be due to thrombosis occurring in the sac of an aneurysm of either the dissecting or saccular type Thrombosis of the abdominal aorta associated with syphilitic aortitis has been reported by Ronald and Leslie (1940) and by Greenfield (1943) Rarely thrombosis may follow pressure upon the aorta from without , Hesse (1921) reviewed 3 cases in which thrombosis was due to pressure by tumours, and Pinkerton (1948) described a case in which a thrombus formed in the aorta where it was compressed by a large osteophyte from the lumbar vertebræ A large embolus may lodge in the aorta and occlude the bifurcation by being compressed into the much narrower common iliac arteries Consecutive thrombosis proximal and distal to the clot completes the block and, much more importantly, makes it irreversible Such emboli originate most often in the heart, either from a thrombus in a fibrillating left auricle or from a mural thrombus formed on the endocardial surface of a myocardial infarct Paradoxical emboli have their origin in the systemic veins and reach the arterial circulation through a defect in either the interventricular or the interatrial septum Thrombi which form in the pulmonary veins may become detached and may be swept into the left side of the heart and thence into the aorta A partly thrombosed aneurysm or a thrombus formed on an atheromatous or syphilitic plaque in a more proximal segment of the aorta is another possible source of an embolus at the bifurcation Among rare types of emboli which have been recorded at the aortic bifurcation are vegetations from an anomalous aortic valve, a clot from a partly thrombosed ductus arteriosus, a portion of a myxomatous tumour of the heart and a 0 45 in calibre bullet

Both sudden and gradual types of occlusion can be recognised Sudden occlusions are usually due to embolism and are associated with an abrupt onset of symptoms indicating acute and severe ischæmia of the lower limbs Gradual occlusions are usually thrombotic in nature and the time at which the obstruction becomes complete is often difficult to determine A patient with this latter type of lesion presents symptoms which, at first, may not even suggest the possibility of a vascular disturbance , only on clinical examination is it discovered that there is occlusion of the abdominal aorta Occasionally it is possible to recognise a third group which may be described as " acute on chronic " Patients in this group are either known to have suffered from occlusive vascular disease of the lower limbs for some years, or give a history which indicates that this has been so , subsequently a sudden incident occurs in which a major proximal vessel, often the aortic bifurcation, is occluded

Collateral Circulation —All the pathological processes we have mentioned reduce the amount of blood passing through the aorta, and we must enquire if there are alternative routes by which blood may reach the viscera and the lower limbs In favourable circumstances, and the favour is time, both the viscera and the limbs can be adequately nourished when the aorta itself and the origins of its visceral branches are occluded

Visceral Collaterals —In 1863 the existence of a subperitoneal arterial plexus was described in detail by the great Edinburgh anatomist, Sir William Turner, when he was Dr Turner and a demonstrator in the Department of Anatomy His summary was as follows —

(1) That in the subperitoneal fat and areolar tissue a system of anastomosing arteries exists of greater extent and importance than has been hitherto generally recognised

(2) That there is a much greater amount of communication between the different branches of the abdominal aorta than is commonly supposed

(3) That not only is it possible to inject the arteries of the abdominal wall from those of the viscera, but that to some extent the blood vessels of one viscus may be injected from those of another, and this not through the main trunk from which they both proceed, but through their mutual communications with an intermediate set of anastomosing arteries

A case showing the functional capacity of these communications between somatic and visceral vessels was published in 1869 by John Chiene, later Professor of Surgery in the University of Edinburgh, when he too was a demonstrator in the Department of Anatomy

There was complete obliteration at their origins of the cœliac, superior mesenteric and inferior mesenteric arteries, and the viscera were supplied thus stomach, liver, spleen, pancreas and duodenum from left intercostals, left renal and suprarenal arteries and left lumbar arteries, cæcum and ascending colon, from right subcostal artery, remainder of intestines, from internal iliac arteries, through a large plexus surrounding the rectum, principally from a branch of the right internal pudendal which joined directly with the right branch of the superior rectal artery (Fig 3) The efficacy of the third of these anastomotic systems depends on the existence of an anastomosis between the left colic branch of the inferior mesenteric artery, and the left branch of the middle colic derived from the superior mesenteric artery Sometimes this anastomosis is absent in man, and it is normal for it to be absent in ruminant animals

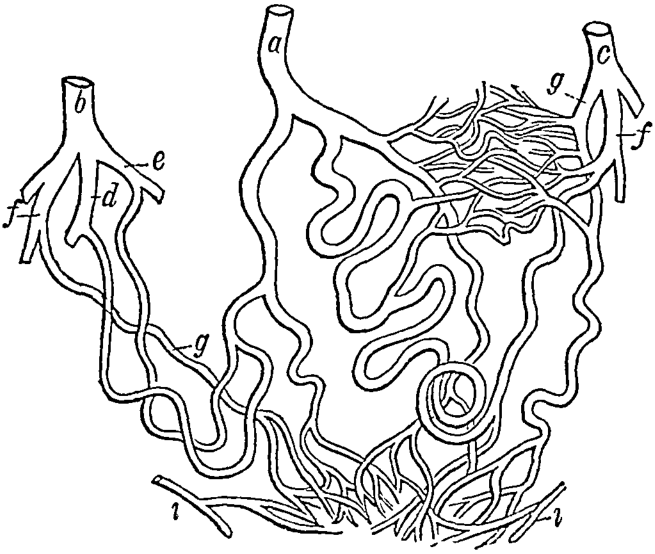

FIG 3 —Diagram of pelvic plexus, seen from behind, the sacrum having been removed (*a*) Superior rectal (*b*) Left internal iliac (*c*) Right internal iliac (*d*) Sciatic (*e*) Gluteal (*f*) Internal pudendal (*g*) Middle rectal (*i*) Internal pudendal in perineum, giving off inferior rectal (After Chiene, 1869)

Somatic Collaterals —When the aorta is blocked at its bifurcation, blood reaches the lower extremities in two ways (1) through the communications between the terminal branches of the inferior mesenteric artery and the branches of the internal pudendal, superior and inferior gluteals, obturator and circumflex arteries (Fig 4) Recently Lindstrom (1950) demonstrated the circulation through these collaterals in the living subject In 2 cases in which the aorta was occluded by a thrombus which did not extend as high as the origin of the inferior mesenteric artery, he showed by aortography that blood was passing to the lower limbs by way of the inferior mesenteric artery and the anastomosis between the superior rectal artery and the middle rectal branch of the internal iliac, the femoral artery was refilled through the anastomoses between the obturator and internal pudendal arteries and the medial femoral circumflex arteries (2) By purely somatic channels which include an *anterior* route, by which the superior epigastric artery communicates with the inferior epigastric, and a *posterior* route, by which the lowest intercostal and the lumbar arteries arising above the block link up with the iliolumbar, deep circumflex iliac, and superior gluteal arteries distal to it (Fig 4) In the female, the ovarian artery also contributes to this anastomosis These vessels may seem to provide an insufficient source of nourishment to the legs, and indeed at best it is precarious But if the aortic block is slowly produced it is enough for the life of the limb, in such cases the greatly enlarged inferior epigastric artery may pulsate so strongly that it may be mistaken for the femoral

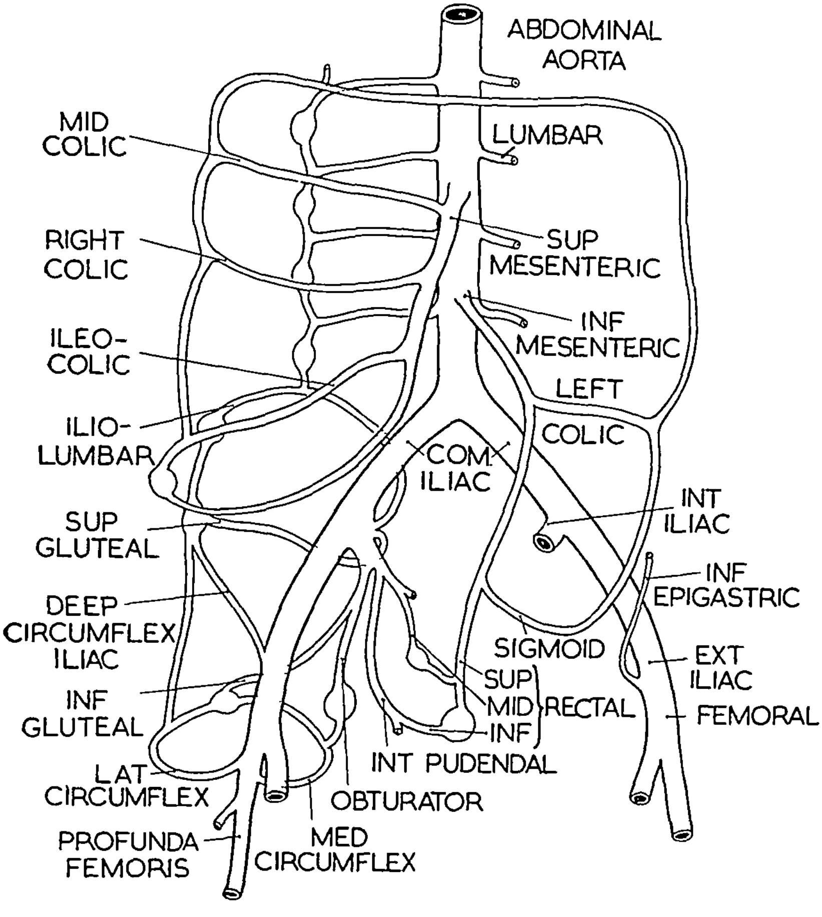

FIG 4—Somatic and visceral anastomoses between abdominal aorta and arteries of lower extremity (Modified from Quiring, D P (1949), *Collateral Circulation* London Henry Kimpton)

PART II—AORTIC THROMBOSIS

In these cases the diagnosis is not so certain as in our cases of aortic embolism, but we have observed 11 patients aged from 35 to 57 years in whom the diagnosis was probably thrombosis of the abdominal aorta In at least one case it is likely that the initial episode was embolic, but at our first examination none of the patients told the dramatic story of acute occlusion of the aortic bifurcation There were 10 males and one female (Table I)

TABLE I

Aortic Thrombosis Details of Cases

Case	Sex	Age	Type of Onset	Presenting Symptoms	Duration
1	M	44	Gradual	Claudication in calves at 50 yds Cold feet	3 years
2	M	47	Gradual	Claudication in calves and thighs at 100 yds Cold feet	2 years
3	M	50	Gradual	Claudication in calves at 80 yds	7 years
4	M	50	Gradual	Right leg amputation 7 years Left leg amputation 5 years Gangrene right stump 3 months	7 years
5	M	50	Gradual	Claudication in calves at 20 yds Cold and numb feet Uselessness of legs	1 year
6	M	56	Gradual	Claudication in calves at 50 yds Rest pain Swelling of ankles	4 years
7	M	57	Gradual	Claudication in calves at 20 yds Night cramps in legs Cold feet	11 years
8	M	52	Acute on chronic	Claudication in calves at 50 yds Night cramps in legs Numbness and loss of power in legs Swelling of legs	2 years and 2½ months
9	M	57	Acute on chronic	Pain in lumbar region Claudication in left leg at ¼ mile Loss of power, coldness and pain in right leg	1 year and 6 months
10	M	35	Episodic	Claudication in calves at 20 yds Cold feet Loss of sensation in feet Burning in feet at night	8 months
11	F	57	Sudden	Loss of power in right leg Claudication in calves and thighs at 20 yds Night cramps in legs Cold feet	1 month

Clinical Observations

(*a*) THE ONSET

In 7 patients the onset was gradual When first seen, 5 of this group had symptoms suggestive of aortic occlusion None was seen less than one year from the onset of symptoms and in one patient symptoms had been present for eleven years In these cases there was a history of claudication beginning in one or both calves, and of progressive shortening of the " claudication distance " The other 2 patients in this group (Cases 3 and 4) had been under observation for seven years , during this period symptoms of arterial occlusion in one leg were followed by similar symptoms in the other leg and later by signs of a proximal extension of the thrombotic process In Case 4

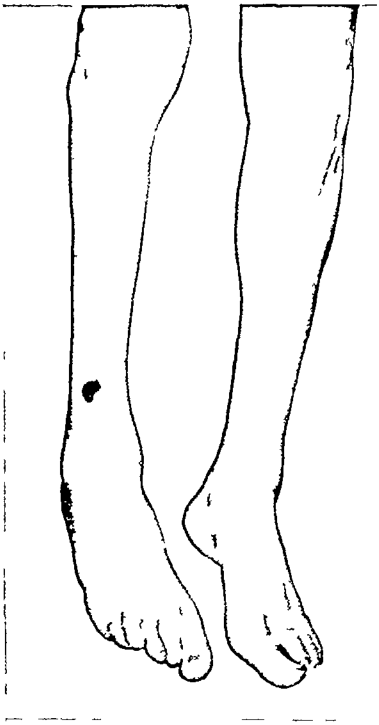

FIG 6 —Aortic thrombosis CASE 9 —To show extreme wasting of right leg which was paralysed

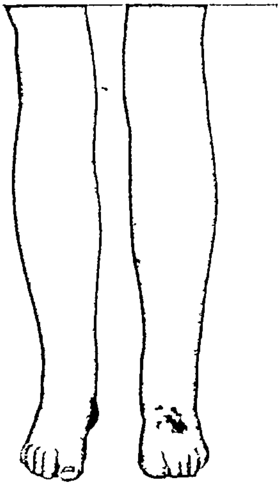

FIG 5 —Aortic thrombosis CASE 8 —To show swelling of legs and minor nutritional changes

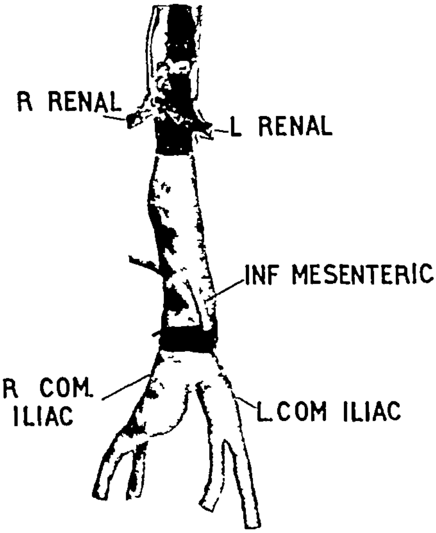

FIG 21 —Aortic thrombosis CASE 8 —To show extent of thrombus

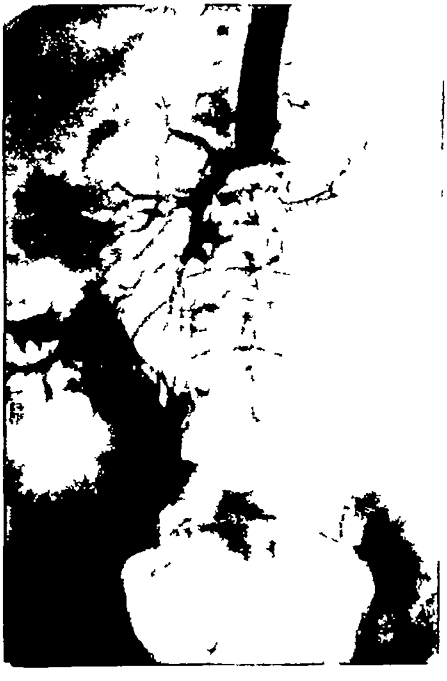

FIG 13 —Aortic thrombosis CASE 1 —Post mortem aortograph to show upper level of thrombus and lack of continuity between renal arteries and aortic lumen

the aortic occlusion was not complete but the case has been included to illustrate its gradual development

Two patients (Cases 8 and 9) had experienced claudication in the calves for months or years when their symptoms suddenly became more severe The first patient, who had had claudication in both calves for two years, awoke to find both feet white and numb, and was unable to move his toes When he hung his legs over the edge of the bed, the feet became red, to the accompaniment of intense paræsthesiæ Later he was able to walk and to work, but when he went to bed his feet again blanched, he lost the power to move his toes and had to sleep sitting in a chair The second patient had been unable to work for six months because of backache and pain in the left calf on exercise Within a subsequent period of two months, he had two episodes of sudden loss of power in the right foot associated with numbness of the toes and cramp in the calf After the second of these incidents the right foot remained persistently cold and painful These 2 cases fall into the group of " acute on chronic occlusion "

In Case 10 the onset was episodic The patient, who suffered from subacute bacterial endocarditis, related two separate incidents in which he had sudden pain, first in the left then in the right leg When he recovered from the endocarditis he found that he was unable to walk more than 20 yards without experiencing pain in both calves, and he noticed that his feet were always cold It would appear that two separate embolic episodes were followed by consecutive proximal thrombosis which reached the aortic bifurcation

Only one patient (Case 11) had a sudden onset One evening while out of doors she felt " all the feeling going out of her right leg " She had great difficulty in walking, had to drag her legs along and was unable to board a tram-car without assistance Subsequently she had claudication in both calves, cramp in both legs at rest in bed, and she complained of cold feet On examination one month after the onset there was no evident source of embolism

(*b*) COMPLAINTS

The most constant complaint was intermittent claudication in the calves It was experienced by all patients and by the time they had come under our care their " claudication distances " on level ground were very short , the longest was 100 yards, the shortest (4 cases) 20 yards Two patients had claudication pain in the muscles of the buttock also, in the territory of the internal iliac artery The next most common symptom was persistent coldness of the feet, of which 7 patients complained Three patients complained of cramp in the legs at rest in bed, severe enough either to prevent sleep or to waken the patient after he had gone to sleep , in 2 of the 3 patients the cramps were associated with a feeling of numbness and loss of power in the limbs and they were relieved if the patient got up and walked about Subjective disturbances of sensation in the feet were noted by 5 patients These included a feeling of numbness, chiefly in the soles, a sensation of " burning " at rest in bed and severe rest pain Four patients remarked upon loss of power, weakness or " uselessness " of their lower limbs Swelling of the legs and feet was noted in 2 cases

(*c*) CLINICAL FEATURES

(1) *Those Directly Related to the Aortic Thrombosis* —Absence of pulses in the lower limbs was the most constant and most important finding In 8 cases pulsation could not be felt in the femoral arteries or in any of the more distal vessels In Case 1 weak femoral pulses were felt and in Cases 4 and 10 a feeble pulse could be felt in the left femoral artery only * Data regarding pulsation in the abdominal aorta and iliac vessels are presented in Table II

TABLE II

Aortic Thrombosis Pulses

Case	Aorta	External Iliac		Femoral *		Additional Pulses
		R	L	R	L	
1	Pulsation in upper epigastrium becoming faint above umbilicus	?	±	?	±	None
2	Present	—	—	—	—	None
3	Pulsation felt high in abdomen , not lower	—	—	—	—	Left circumflex iliac
4	Present	—	+	—	+	None
5	Felt to 0 5 cm below xiphoid only	—	—	—	—	None
6	N R	N R	N R	—	—	N R
7	Pulsation stopped 3 cm above umbilicus	—	—	—	—	None
8	N R	?	?	—	—	None
9	Pulsation stopped 2 3 cm above umbilicus	—	—	—	—	None
10	Obese Pulse not felt	—	+	—	±	None
11	Pulsation stopped 2 cm above umbilicus	—	—	—	—	None

N R = No record ? = Doubtful pulse ± = Weak or faint pulse
+ = Normal pulse — = Absent pulse

* Pulsation was absent distal to the femoral arteries in all cases

In addition to absence of pulses, other signs of vascular insufficiency were present (Table III) The feet were cold to the touch In one case (Case 5) pallor of the feet was present even when the patient stood erect In all cases in which the effect of raising and lowering the feet was tested, marked pallor on elevation and either cyanosis or rubor on dependency were recorded Four patients had œdema of one or both legs , in one of these there was gross swelling of the feet and legs and blistering of the skin of the feet (Fig 5) In 8 cases the nutrition of the

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* In Case 10 after lumbar sympathectomy the amplitude of this pulse was improved

TABLE III

Aortic Thrombosis Vascular Disturbances in Lower Limbs

Case	Temperature of Feet	Skin Colour of Feet			Œdema	Nutrition
		Horizontal	*Elevated*	*Pendent*		
1	Cold	Cyanosed	Pallor	Rubor rt ++ lt +	None None	Good Good
2	Cool	Normal	Gross pallor	Rubor +	None	Good
3	Warm	Rubor	Moderate pallor	Rubor +++	None	Good
4	Both lower limbs amputated					Gangrene rt stump
5	Cold	Pallor	Pallor	Rubor +	None	Fair
6	N R	N R	N R	N R	+	No gangrene
7	Cold	Pink	Pallor	Rubor +	None	Fair
8	Cool	Pale	Pallor	Cyanosed +	+++	Blisters
9	Rt cold Lt warm	Rt rubor Lt pink	Pallor rt ++ lt +	Rubor rt +++ lt +	Rt + Lt none	Gangrene of rt heel and leg
10	Cold	Cyanosed	Pallor	Rubor rt + lt ±	Rt + Lt ++	Good Good
11	Cold	N R	N R	N R	None	Good

TABLE IV

Aortic Thrombosis Neurological Disturbances in the Lower Limbs

Case	Wasting	Fasciculation	Power	Reflexes *	Sensation
1	+E D B	Present	Good	K J's ++ A J's ±± Plantars ↓ ↓	Hypæsthesia and hypalgesia of toes
2	General	Present	Normal	All normal	Normal
3	None	Present on rt	Good	All normal	Normal
4	Both lower limbs amputated				
5	N R	N R	Normal apart from E D B on rt = o	All normal	Lt "sock" loss Rt "carpet slipper" loss
6	N R	N R	N R	N R	N R
7	+E D B	Ant and post tibial groups rt and lt	Good	All normal	Normal
8	None	None	Good	K J's ++ A J's −− Plantars ↓ ↓	Hyperpathia of soles †
9	Rt thigh + Rt leg +++	Present lt calf	Gross weakness below rt knee	K J's ++ A J's −+ Plantars o ↓	Rt sciatic loss
10	N R	None	Weakness below knees	K J's ++ A J's −− Plantars ??	Bilateral "stocking" loss
11	None	Ant and post tibial groups rt and lt	Good	All normal	No loss

N R = No record E D B = Extensor digitorum brevis

* Reflexes are given for right and left legs respectively

Knee and Ankle Jerks — + = Normal reflex ± = Diminished reflex — = Absent reflex

Plantars — ↓ = Flexor response o = No response ? = Doubtful response

† In this case elevation of the feet produced an area of sensory loss over the fore feet which recovered when the feet were returned to the horizontal (see Fig 7)

feet was good, only minimal changes in the nails and in the texture of the skin and some atrophy of the pulp of the toes being present Three patients showed gangrene or pre-gangrenous lesions One (Case 4) who had had both legs amputated because of gangrene seven and five years before, was re-admitted with patchy gangrene of the right stump The second (Case 8) was the patient who had gross swelling of the feet, in whom the blistered areas of skin later formed necrotic sloughs, in the third (Case 9) there were patches of gangrene on the right heel and on the front of the right leg (Fig 6)

In most of the cases neurological disturbances of varying severity were present (Table IV) Generalised wasting of the muscles of the lower limbs and fasciculation in the muscles of the thigh, calf, anterior tibial group and small muscles of the foot were often noted One patient (Case 10) had weakness of the muscles below both knees, thought to be hysterical In 2 patients (Cases 8 and 10) both ankle jerks were absent and, in a third case (Case 1) they were diminished Five patients had some loss of sensation The patient (Case 10) who was thought to have hysterical weakness of the muscles of the legs had "stocking" areas of analgesia Another patient (Case 5) had an area of anæsthesia over the foot and lower third of the leg on both sides, and analgesia of the distal parts of both feet One patient (Case 1) had hypæsthesia and hypalgesia of the toes only In Case 8 when the patient was horizontal only slight hyperpathia of the soles was noted, but when the feet were elevated by raising the foot of the bed on 9-in blocks, in an effort to reduce œdema, they blanched and overnight an area of anæsthesia

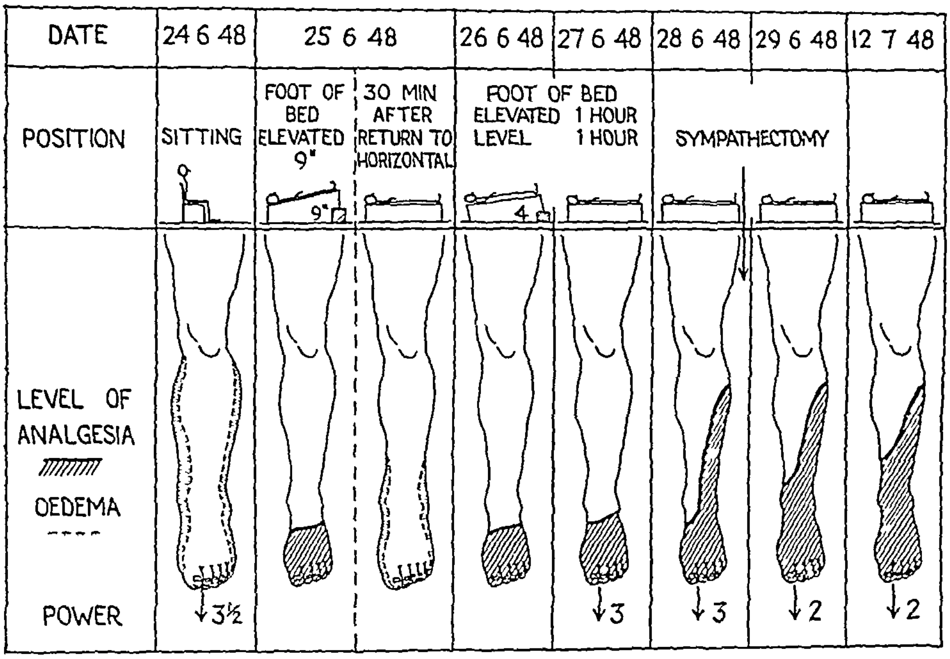

Fig 7 —Aortic thrombosis Case 8 —To show variations in swelling and sensory level in various positions and at different dates (Full power of flexion of foot = 5)

and analgesia became detectable (Fig 7), this quickly disappeared when the blocks were removed

Neurological signs were most prominent in Case 9 This patient had a right drop-foot with contractures of the muscles of the calf and of the long extensors of the toes The muscles below the right knee were grossly wasted and fibrotic, the peronæi were paralysed and the other muscles of the leg showed only feeble voluntary power The area of sensory loss corresponded to the distribution of the right sciatic nerve We believe that such neurological findings are exceptional, and that they were the result of embolic occlusion of the right popliteal artery *

TABLE V

Aortic Thrombosis Cardiovascular System

Case	Blood Pressure	Heart	Arteries	Urine
1	144/ 84	Clinically—soft mitral systolic murmur E C G —inversion of T 3 Pathol —coronary atheroma	Calcified external iliac arteries	N A D
2	200/110	Clinically—angina of effort —aortic systolic murmur E C G —myocardial damage	Occlusive vascular disease rt arm Calcified vessels in thighs	N A D
3	130/ 80	Clinically—normal E C G —normal		N A D
4	Max 146/60 Min 112/50	Clinically—normal E C G —coronary ischæmia Pathol —myocardial infarction	Calcified thoracic and abdominal aorta Occlusive vascular disease rt arm	N A D
5	200/110	Clinically—mitral systolic murmur Pathol —slight hypertrophy and dilatation only	Nicking of retinal veins	N A D
6	Max 180/105 * Min 125/ 80 *	Clinically—enlarged heart —congestive failure E C G —no definite abnormality Pathol —hypertrophy and dilatation	Narrowing of retinal arteries	Slight pyuria only
7	170/ 80	Clinically—N A D E C G —normal	Calcification in dorsalis pedis artery	N A D
8	150/ 92	Clinically—N A D Pathol —myocardial infarct —coronary atheroma		N A D
9	150/ 90	Clinically—mitral systolic murmur E C G —within normal limits	Calcified and dilated abdominal aorta	N A D
10	115/ 76	Clinically—mitral stenosis —aortic incompetence E C G —normal		Trace of albumin
11	174/110	Clinically—normal E C G —normal	"Silver wiring" of retinal arteries Calcified aorta and iliac arteries	N A D

* Observations made over a period of 14 weeks

(ii) *Those Indicating Generalised Cardiovascular Disease*—The majority of the patients had definite evidence of general disease of the cardiovascular system (Table V) The blood pressure was elevated in 4 cases, was at the upper limit of normal in 3 cases and could be regarded as normal in only 4 cases In 3 patients there was clinical evidence of heart disease In Case 2 there was angina on effort, a loud aortic systolic murmur and electrocardiographic evidence of myocardial damage, in Case 6 there had been several episodes of congestive cardiac failure, the cause of which was undetermined, in Case 10 there had been an attack of subacute bacterial endocarditis superimposed on mitral stenosis and aortic incompetence In Cases 4 and 8 the heart was considered to be normal on clinical examination, later both patients died from cardiac failure, at autopsy myocardial infarction and advanced atheroma of the coronary arteries were found In Case 1 also autopsy disclosed unsuspected coronary atheroma In Cases 2 and 4 there was evidence of occlusive vascular disease affecting the right upper limb, shown in Case 2 by claudication in the biceps muscle, absence of the brachial pulse and a feeble radial pulse In Case 4 pulsation was absent in the distal third of the right brachial artery but good pulsation was felt in the profunda and ulnar collateral arteries, at the wrist the ulnar pulse was present, the radial absent In 2 patients (Cases 7 and 11) arteriosclerosis of the retinal vessels was present

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* Later the limb was amputated and dissected, the femoral artery was patent but the popliteal artery was occluded by an embolus, infarcts were present in tibialis anterior and peronæus longus

(*d*) SPECIAL INVESTIGATIONS

(1) *Circulation in the Lower Limbs*—Oscillometric readings of pulsation at the ankle were attempted in 6 cases, with the instrument used, the normal reading varied from 1 5 to 4 units In the cases of aortic thrombosis the maximum recorded was 0 75 units (at the right ankle in Case 5) and in 2 cases oscillations were absent In Case 9 the cuff of the oscillometer was applied to the thighs, even at this level the maximum reading was 0 6 units In 5 patients (Cases 1, 3, 7, 9 and 10) vasodilatation tests were performed (Table VI) It will be noted that in 4 of these the skin temperature of the toes did not reach 30° C and the blood flow through the feet was below normal levels In Case 3 the feet remained persistently warm (32 5° C) although the maximum blood flow was low In Case 10 before sympathectomy a recording of blood flow in the feet could be obtained only when the collecting cuff pressure was considerably less than the diastolic pressure in the arms, an indication that arterial pressure in the legs was low (Fig 8)

The response to exercise was investigated in 5 cases (Cases 1, 2, 7, 9 and 10) None of the patients was able to perform a standard exercise test—plantar flexion of the foot against a weight of 6 lb at a rate of 100 excursions in two minutes In 4 cases the resting blood flow in the legs was low, and although attempts were made to obtain records after such mild exercise as the patients were able to perform, the records were unsatisfactory The response to exercise was undoubtedly poor in all cases In Case 2 a substitute test was used, "walking on the spot" for one minute Before exercise the blood flow through the leg was low and the tracing did not show pulsation (Fig 9) During exercise the patient complained of pain in the calves and the feet blanched After exercise the pain and the pallor continued for two minutes During the first minute after exercise the blood flow

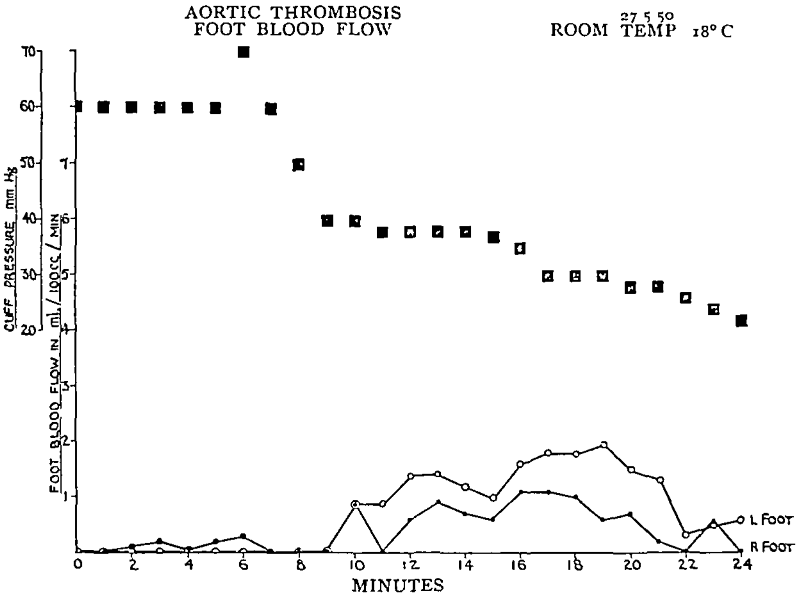

Fig 8 —Aortic thrombosis Case 10 —To show variations in foot blood flow at different pressures of occlusion cuff

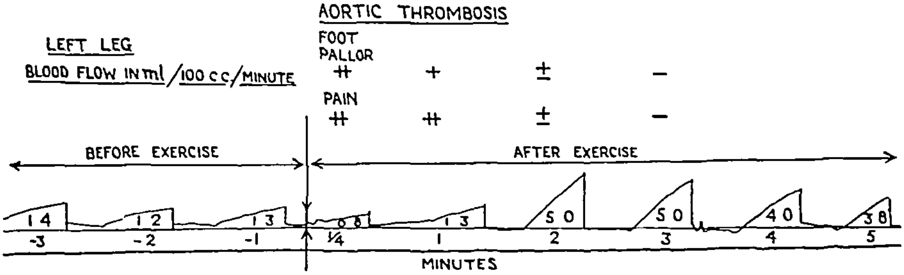

Fig 9 —Aortic thrombosis Case 2 —To show flow of blood in one leg before and after exercise

in the leg was low, it rose to a maximum at two minutes and thereafter slowly returned to the resting level (Fig 10) This finding is similar to that recorded by Shepherd (1950) in patients suffering from occlusive vascular disease who have severe intermittent claudication

(ii) *Aortography* —In 5 cases attempts were made to visualise the obstruction at the aortic bifurcation by injecting an opaque medium * into the aorta above the level of the block. In 4 cases this was done at the same time as lumbar sympathectomy was performed. On the whole, these attempts were not successful. In Cases 1 and 2, pulsation in the aorta could not be felt until just below the diaphragm. The injections were made at this level but only the renal circulation and later the pelves and calyces were outlined. In Case 5, the injection was made into a non-pulsatile portion of the aorta at the level of the second lumbar vertebra; the radiograph showed only a few small vessels in the muscles of the back and abdominal wall. The most satisfactory aortograph was obtained in Case 8 (Fig. 11); pulsation was felt at the aortic bifurcation and in the right common iliac artery; the aortograph confirmed that the bifurcation and right common iliac artery were patent. The right external iliac artery was completely occluded and there was evidence of a poor collateral circulation in the right side of the pelvis.

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* Fifty per cent perabrodil or diadone

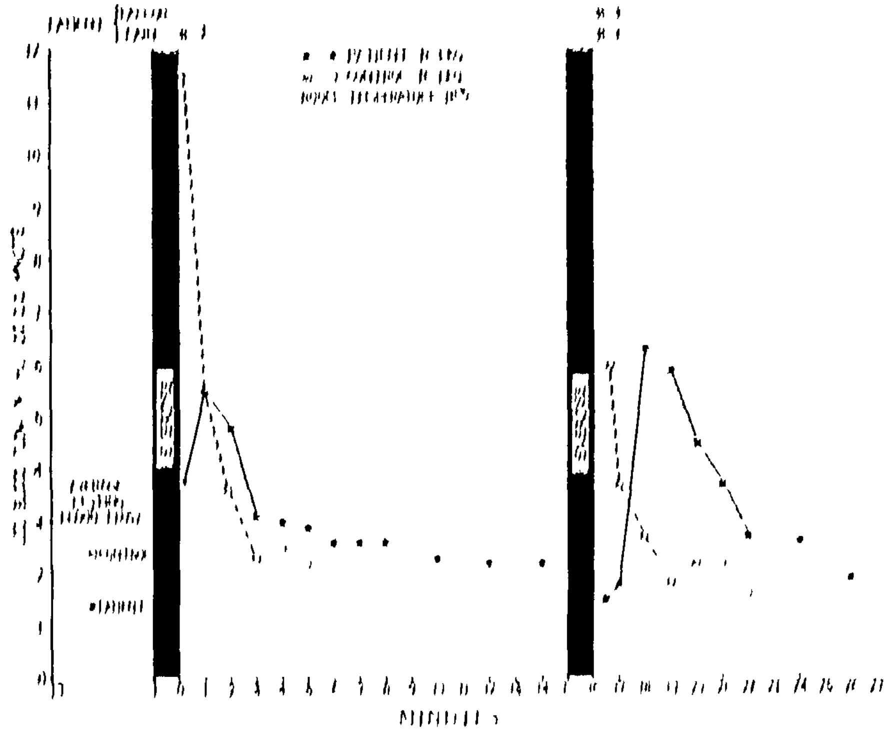

Fig. 10.—Aortic thrombosis. Case 1. To show delay in return to resting blood flow after exercise.

(iii) *Miscellaneous.* Serological tests for syphilis were done in 8 cases and all were negative. We have no reason for thinking that syphilis could have been an aetiological factor in the other 3 cases.

In 5 cases radiographs of the abdomen and lower limbs revealed calcification in the walls of the larger arteries, in 3 cases calcification was not seen and in the remaining 3 cases radiographs were not taken.

(*e*) TREATMENT AND PROGRESS

Four patients underwent bilateral lumbar sympathectomy, in 2 cases (Cases 2 and 7) the operations were done in two stages through lumbar incisions, and in 2 (Cases 1 and 10) both chains were dealt with through a transperitoneal approach Two patients (Cases 5 and 8) had only a left lumbar sympathectomy, both died before the second operation One patient (Case 11) received two intrathecal injections of alcohol to relieve severe rest pain One patient (Case 9) had a right supracondylar amputation performed because of gangrene In Case 4, both legs had been amputated previously because of peripheral arterial occlusion (Fig 12), at a later date signs appeared suggesting proximal

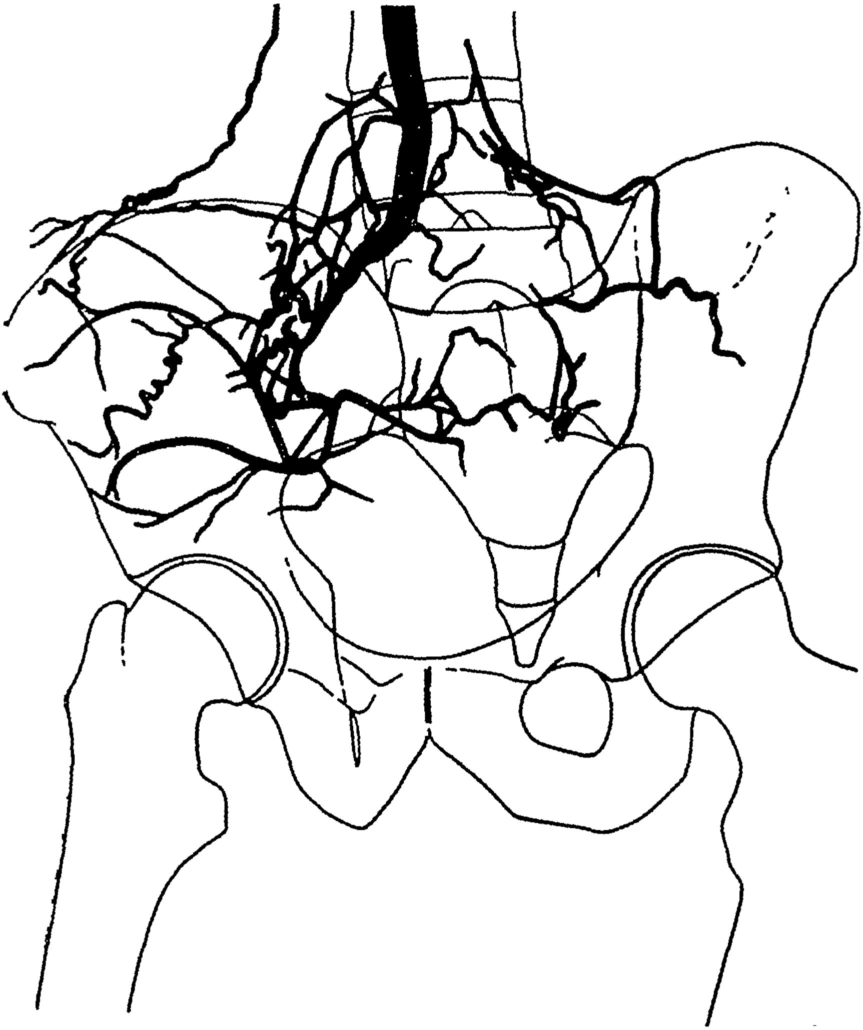

FIG 11 —Aortic thrombosis CASE 8 —Tracing of aortograph to show partial filling of right common iliac artery

extension of the disease and disarticulation at the right hip had to be performed The remaining 2 patients (Cases 3 and 6) received no special treatment, in one of these (Case 6) the diagnosis was not made before death

The results of sympathectomy have been disappointing Three patients (Cases 1, 5 and 8) died within one month of the operation before any clinical assessment of its effect could be made In the remaining 3 cases (Cases 2, 7 and 10) there was no good evidence that intermittent claudication, which was the disabling symptom in all 3, was helped by the operation On the other hand, vasomotor studies on 4 patients (Cases 1, 2, 7 and 10) after sympathectomy indicated that the blood supply to the feet was improved (Table VI)

TABLE VI

Aortic Thrombosis Vasomotor Studies

Number	Age	Room Temperature ° C	Limb	Before Sympathectomy				After Sympathectomy		
				Toe Temperature ° C		Foot Blood Flow ml /100 c c /min		Time Months	Toe Temperature C° Average Resting	Foot Blood Flow ml /100 c c /min Average Resting
				Average Resting	Maximum	Average Resting	Maximum			
1	44	18 20	L	26 5	27 0	3 2	3 3	¼ and ⅓	27 0	4 5
			R	27 0	27 8	1 3	1 5		24 0	5 1
2	47	18	L					4 and 11	17 4 *	3 4
			R						24 6	3 2
3	50	21	L	32 5	31 0	3 2	3 0		No sympathectomy	
			R	32 5	32 0	3 4	5 4			
7	57	18 19	L	21 2	25 3			8	30 8	4 9
			R	21 3	24 0				30 2	4 5
9	57	17 5	L	25 5	22 5				No sympathectomy	
			R	21 5	19 0					
10	35	18 20	L	21 8	28 5	1 4		1½		8 7
			R	22 8	28 8	0 9				10 6
Control †	20 43	17 23	Average of 10	21 7	34 7	3 5	19 6	½ 1½	32 2	8 7
			Range	*17 1 24 3*	*33 6 35 0*	*1 5 7 0*	*13 0 30 8*		*28 9 34 5*	*3 5 18 0*

* Reading made two months after another episode of arterial occlusion in left leg The blood flow record in the next column was made seven months later

† Average of 10 limbs in 5 cases of acrocyanosis with normal pulses

At the time of writing, 6 patients have died and 5 are alive The deaths occurred as follows —

CASE 1 —Immediately after sympathectomy his feet were warm and pink, the veins were well filled and the hypæsthesia and hypalgesia of the toes disappeared One week after operation he began to cough and brought up considerable quantities of sputum, albuminuria was noted and the blood urea began to rise On the eleventh day the feet were noted to be cold and during the next forty-eight hours the coldness spread proximally to the knees On the sixteenth post-operative day he died

CASE 2 —This patient was not greatly improved by a high bilateral lumbar sympathectomy Two months later he had an episode in which further thrombosis in the left lower limb occurred At best he could walk only 50-60 yards and his activity was restricted not only by the state of his lower limbs but also by angina of effort and exertional dyspnœa Fifteen months after sympathectomy he died suddenly at home

CASE 4 —The clinical progress of this patient is illustrated in Fig 12 Following the disarticulation at the right hip on 30 1 51, his condition gradually deteriorated, the operation wound failed to heal, he became grossly œdematous and died five months later from cardiac failure

DATE	FEBRUARY 1944	MARCH 1946	DEC 1946-MAR 1947	JANUARY 1951	JUNE 1951
AGE	43	45	46	50	50½
SYMPTOMS	SUDDEN ONSET OF PAIN IN RT CALF FOLLOWED BY CLAUDICATION PAIN IN RT FOOT	PAIN IN LEFT FOOT AT REST AND ON EXERCISE	PAIN IN LEFT FOOT AT REST AND ON EXERCISE CLAUDICATION IN CALF AT 50 YD	GANGRENE OF RT STUMP PAIN IN RT STUMP	GANGRENE OF RT STUMP

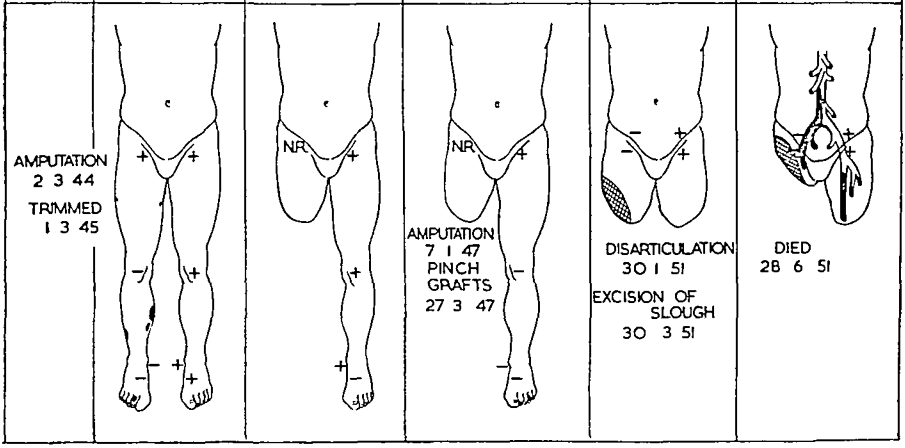

FIG 12 —Aortic thrombosis CASE 4 —Life history of patient suffering from aortic thrombosis over a period of seven years

CASE 5 —The patient died forty-eight hours after left lumbar sympathectomy had been performed The circulation in the left lower limb became worse after the operation and he experienced much pain in this leg He suddenly became dyspnœic, collapsed and died At autopsy right bronchopneumonia and bilateral pulmonary œdema were found

CASE 6 —A diagnosis of aortic thrombosis was made incidentally in a patient who was seriously ill with congestive cardiac failure from which he died

CASE 8 —For four days this patient was treated by elevation of the lower limbs to reduce the œdema It was found that he would not tolerate high elevation of the feet because pallor and paralysis developed With moderate elevation, however, the œdema was much reduced but the area of sensory loss increased Left lumbar sympathectomy was then performed After the operation the condition of the left lower limb became worse It was cyanosed and weak, and insensitive below the knee (Fig 7) and there was considerable residual pain in the leg Fifteen days after operation he had a sudden attack of dyspnœa without precordial pain Twelve days later he had an attack of precordial pain and pericardial friction was noted He died one month after operation, the clinical diagnosis being myocardial infarction At autopsy this was confirmed , there was also fibrino-purulent pericarditis, bilateral pleurisy and œdema and congestion of the lungs with infarcts in both lower lobes

Two of the male survivors (Cases 7 and 10) have had bilateral lumbar sympathectomy , the intervals since operation are fourteen months in Case 7 and seventeen months in Case 10 Intermittent claudication is still a serious disability to both patients , neither can walk more than 50 yards The nutrition of their feet remains good although it is eleven years and two years respectively since their initial symptoms Of the remaining male patients, one (Case 9) within a year of the onset of symptoms had his right leg amputated and in the other (Case 3) the diagnosis of aortic thrombosis has been made within recent months , his progress cannot yet be reported

The only female patient in the series (Case 11) had two intrathecal injections of alcohol (one in February 1949 and the second in July 1949) to relieve severe rest pain She is now (June 1951) able to walk distances up to 100 yards and to do her own housework The nutrition of her lower limbs remains good but she suffers from attacks of cramp in the right leg When she was seen in one of these it was noted that blanching of the right foot accompanied the pain , this suggests that vasospasm may contribute to the attacks

Pathological Observations

In 5 of the fatal cases autopsies were performed and the state of the abdominal aorta and main arteries of the lower limbs was determined

CASE 1 —The thoracic aorta was injected with 50 per cent perabrodil and a radiograph (Fig 13) showed the conical end of the thrombus just proximal to the origin of the superior mesenteric artery The latter was well filled Both renal arteries and their main branches were clearly outlined but there was no apparent connection between the aorta and the renal arteries The arteries in the pelvis and in the lower limbs were not filled Some of the lower intercostal arteries were outlined but there was no evidence of hypertrophy to suggest that these had formed part of a collateral circulation to the lower limbs

When the aorta was examined it was found that proximally the thrombus extended above the renal arteries to the cœliac axis , the latter artery and the superior mesenteric artery were patent Distally the thrombus extended a few millimetres beyond the origin of the right external iliac artery and 2 cm beyond the origin of the left external iliac artery , both femoral and both popliteal arteries were patent The internal iliac arteries were blocked by old thrombus Beyond their origin from the aorta the lumbar arteries, inferior mesenteric artery and middle sacral artery were patent (Fig 14) The walls of the thoracic aorta and external iliac arteries were noted to be atheromatous but the walls of the femoral arteries and the popliteal arteries were healthy The iliac, femoral and popliteal veins were normal

After the aorta and its branches had been fixed in a state of distension, the specimen was split longitudinally into anterior and posterior halves (Fig 15).

The thrombus in the aorta extended from the bifurcation to the level of the cœliac axis The proximal end was convex and extended higher posteriorly than anteriorly, thus a funnel-shaped opening leading to the superior mesenteric artery was formed At the level of the renal arteries an irregular transverse channel lined by smooth clot connected the orifices of the renal arteries This channel communicated posteriorly with one or both of the second lumbar arteries The clot *surrounding the channel* appeared *to be of* more recent origin than the remainder of the thrombus

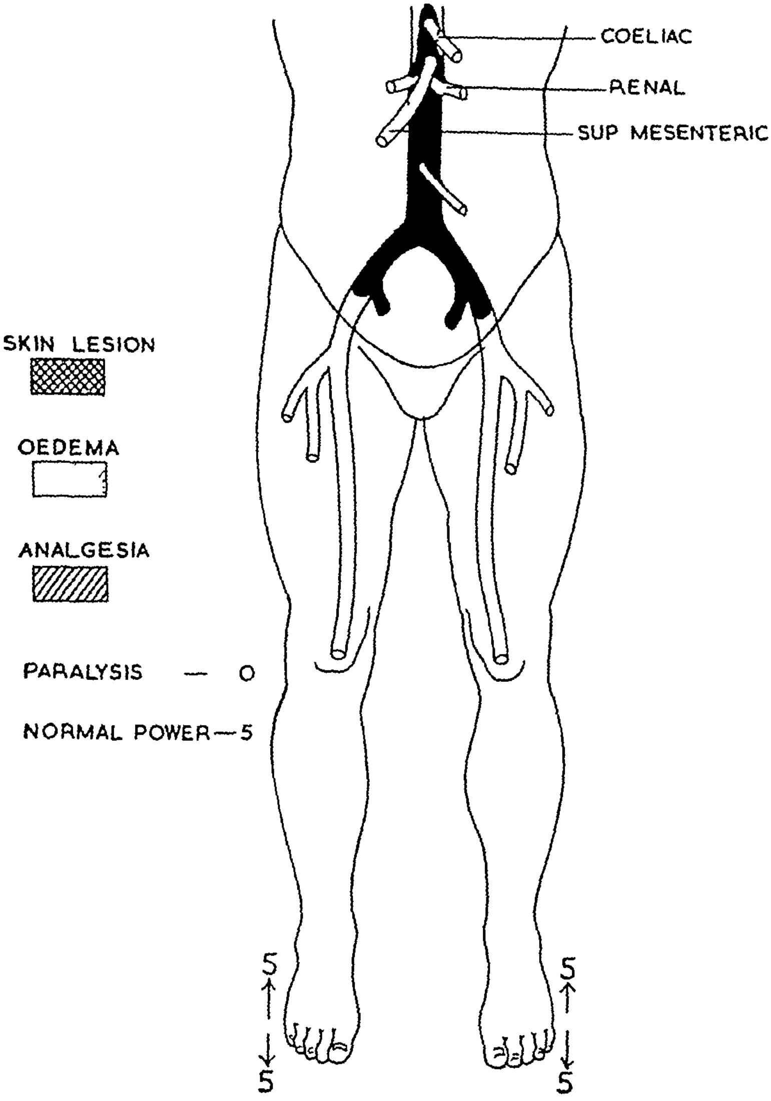

FIG 14 —*Aortic thrombosis* CASE I —*To show extent of thrombus and absence of changes in lower extremities* (Compare Fig 13)
(Figures above and below arrows indicate power in dorsiflexors and plantar flexors respectively)

When these findings are correlated with the curious appearance in the post-mortem aortograph (Fig 13) in which connections between the aorta and the renal arteries seemed to be absent, they suggest that the renal arteries were filled only during systole by way of a narrow channel between the thrombus and the wall of the aorta, during diastole the aortic wall would lie against the thrombus (Fig 16)

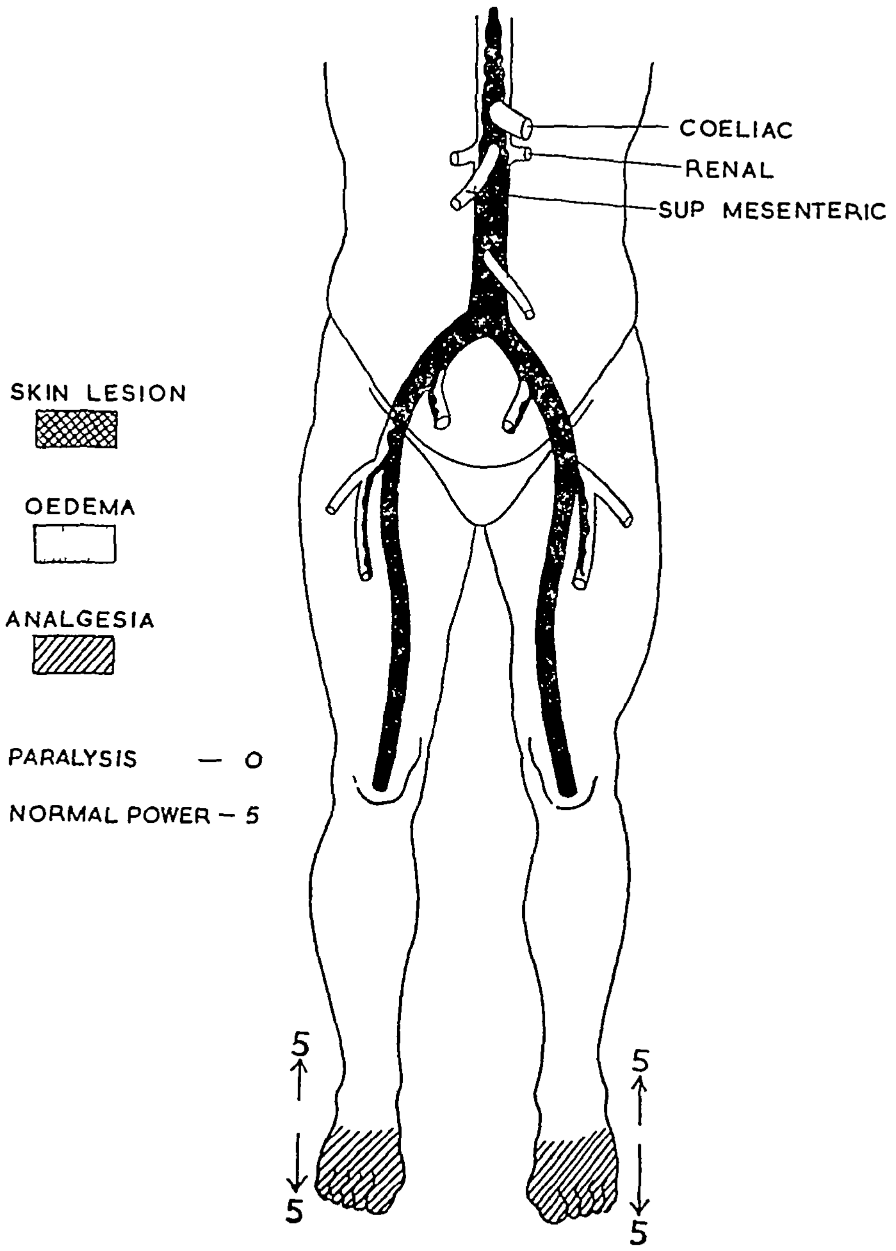

FIG 19—Aortic thrombosis CASE 5—To show extent of thrombus and minimal changes in lower extremities

CASE 4—The abdominal aorta was partially occluded by red adherent thrombus from a point 2 cm distal to the renal arteries to its bifurcation The somewhat sinuous but smooth-walled channel through this clot lay chiefly to the left and communicated with the left common iliac artery which was patent (Fig 17) On the right, the origin of the common iliac, this vessel itself and its terminal branches were completely occluded by organised clot The cœliac, superior mesenteric and renal arteries were patent The inferior mesenteric artery, although blocked at its origin by the aortic clot, was itself patent Gross calcification was present in the walls of the thoracic and

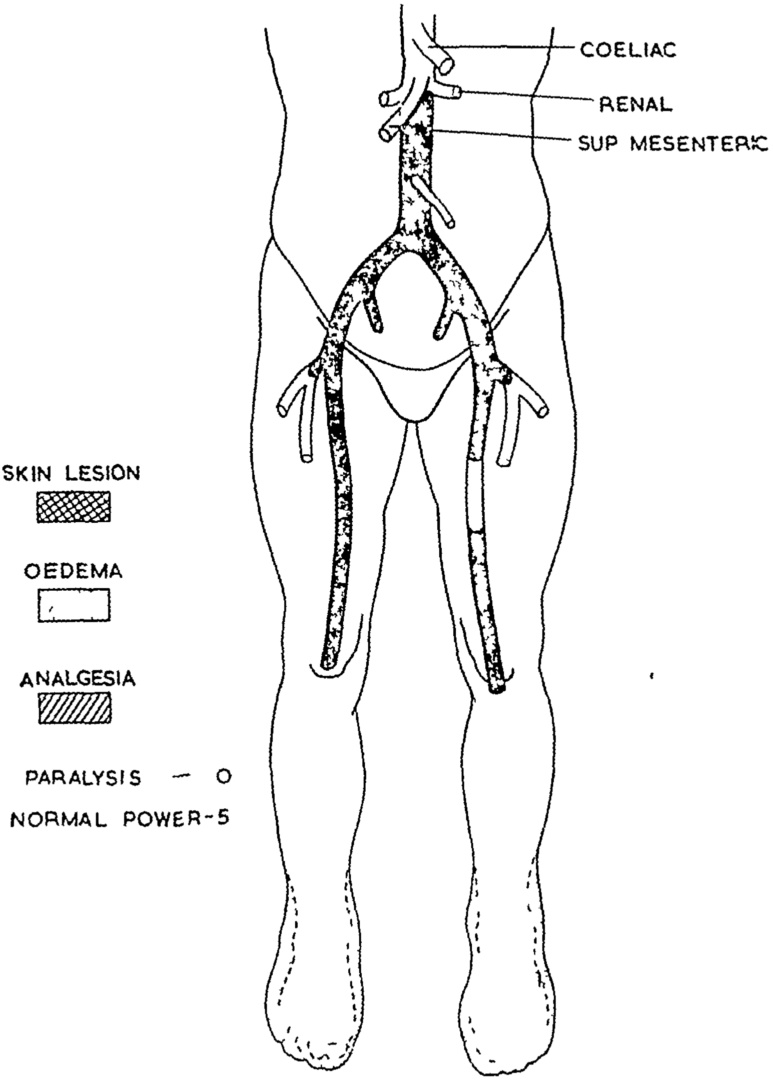

Fig 20 —Aortic thrombosis Case 6 —To show extent of thrombus and changes in lower extremities (No record of power)

abdominal aorta, the cœliac, superior mesenteric and iliac arteries

Case 5 —The proximal end of the thrombus in this case extended 2 cm above the origin of the cœliac artery At this level the block was incomplete and the thrombus was adherent to the postero-lateral wall of the aorta, the block became complete below the renal arteries (Fig 18) The renal arteries, superior mesenteric artery and cœliac axis were patent The common iliac arteries were both completely occluded (Fig 19) and on both sides thrombus was continuous as far distally as the popliteal arteries Calcification was present in the walls of both common iliac arteries

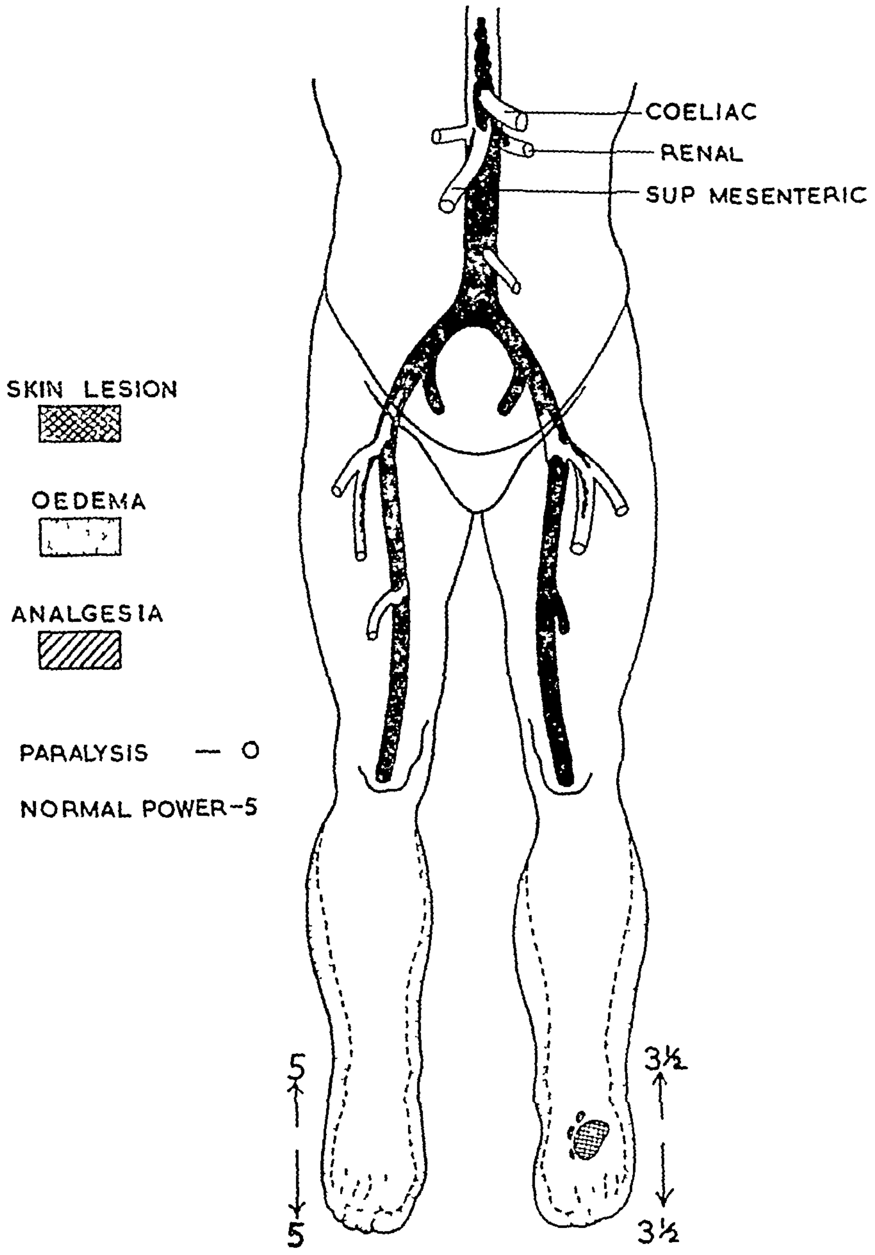

FIG 22 —Aortic thrombosis CASE 8 —To show extent of thrombus and changes in lower extremities

CASE 6 —The aorta was completely blocked to the level of the renal arteries which were patent The arteries of the lower limbs were occluded from the popliteals proximally, on the right the occlusion was continuous through the femoral and iliac vessels to the aortic bifurcation, but on the left a segment of the femoral artery in Hunter's canal was free from thrombus (Fig 20) Only the upper portion of the thrombus was recent , the remainder was pale, reddish-brown thrombus of considerable age The vessel walls showed only a slight degree of calcification

CASE 8 —In this case the thrombus extended above the cœliac axis but at that level did not completely occlude the aortic lumen The cœliac and superior mesenteric arteries were patent There was an old organised thrombus on the right side of the aorta which was not filling the entire lumen and had not occluded the right renal artery (Fig 21) Over this lay more recent red friable thrombus which had completed the occlusion of both aorta and left renal artery This must have formed subsequent to the aortograph made four weeks before death (Fig 11) Both common iliac arteries and the femoral and popliteal arteries were occluded (Fig 22)

DISCUSSION

Only within the last ten years has it been recognised that thrombosis of the aorta can occur insidiously and present a clinical picture which does not suggest a vascular catastrophe Leriche (1940) first described the syndrome and discussed its treatment by lumbar sympathectomy and resection of the aortic bifurcation In subsequent publications (Leriche, 1946 , Leriche and Morel, 1948) he has amplified his views on the subject and reported further examples Since Leriche's original description, a number of continental (*e g* Morel, 1943 , Martorell, 1946) and American (*e g* Holden, 1946 , Price and Wagner, 1947 , Ortner and Griswold, 1950) writers have recognised the syndrome and have reported cases, but the condition has not yet been discussed in British medical literature *

This insidious type of aortic thrombosis is not a rare condition , within a period of twenty months, Elkin and Cooper (1949) saw 10 cases and Milanes *et al* (1950) have recently reported a series of 13 cases Statistics compiled from autopsy material, in which it was often difficult to separate cases of embolism from cases of thrombosis of the aorta, tended to suggest that aortic thrombosis occurred more often in women than in men (Hesse, 1921 , Rothstein, 1935 , Reich, 1943) Since the recognition of the clinical picture of the insidious type, it has become apparent that like other forms of occlusive vascular disease aortic thrombosis occurs predominantly in males Indeed the female patient reported in the present series is only the fourth † in the literature since 1940 , Delannoy (1945) described the condition in a woman of 41 and Milanes *et al* (1950) have two females in their series The condition is not essentially a senile one It occurs most often in the fifth and sixth decades but has been reported in patients as young as 29 years and as old as 69 years The features originally described by Leriche were —In the male, inability to maintain a stable erection because of reduced blood flow through the internal pudendal arteries , extreme fatiguability of the lower limbs , global atrophy of the lower limbs , absence of nutritional changes in the skin and nails, and pallor of the feet even when the patient was standing

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* Since this paper went to press, Goodwin, J F , and Petrie, E (1951), *Brit Heart Journ* , 13, 554, have described a case and discussed the condition

† A fifth female patient was reported by Straus *et al* (1946) but in this case the aortic thrombosis was more acute and was probably related to a course of radio therapy given for a supposed carcinoma of the cervix and to subsequent pelvic sepsis

None of our male patients complained spontaneously of the first of these symptoms and on systematic enquiry not all admitted impotence Elkin and Cooper (1949) found that only five of their 10 patients were unable to maintain a stable erection Impotence may not occur in those cases in which the internal pudendal artery is refilled through collateral channels Leriche stressed that the difficulty with the lower limbs was not true intermittent claudication, but extreme tiredness coming on rapidly when the patient walked and sometimes occurring even when he was standing In our cases the presenting complaint appeared to be typical intermittent claudication in the muscles of the calf of the leg appearing after very short distances The pain seemed to take longer (up to ten minutes) to pass off than in cases of intermittent claudication caused by obstruction of the femoral or popliteal artery The patients were always aware that both legs were affected, whereas the patient who has separate episodes of occlusion affecting first one popliteal or femoral artery and then the other will usually state that the pain affects only the more recently affected limb If the source is not an osteo-arthritic hip joint, complaint of pain on exertion in the muscles of the buttock or thigh should always raise the suspicion of high vascular occlusion Intermittent claudication in the gluteal muscles is an important symptom because it indicates that the internal iliac artery is occluded

Of the other symptoms noted in our cases, coldness of the feet cannot be considered of diagnostic value It is a complaint of all patients who have occlusive arterial disease and of many who have not The occurrence of cramps in the legs at night associated in some cases with pallor of the feet and paralysis has not so far as we are aware been previously described in cases of aortic thrombosis Presumably these symptoms are due to the low blood pressure in the collateral vessels supplying the lower limbs When the patient lies down, the head of pressure is no longer sufficient to maintain the already precarious blood supply , warning symptoms appear which are relieved when he rises and walks about Paræsthesiæ, numbness, pain and other subjective sensory disturbances are due to ischæmic neuritis , it is surprising that the typical pains of ischæmic neuritis described by Goldsmith and Brown (1935) have so seldom been noted in cases of aortic thrombosis Only one of our patients (Case 8) had pain of this nature but the ischæmic neuritis was unilateral and probably due to the previous lodgement of an embolus in the popliteal artery

The most important sign is the absence of pulsation in the arteries of the lower limbs, especially in the femoral arteries In any patient who complains of pain in or fatiguability of the lower limbs, even if the appearance of the limbs does not suggest that the symptoms are of vascular origin, the femoral pulses should always be palpated Often it is difficult to be certain whether pulsation is present in the popliteal and pedal arteries, but normally the femoral pulse is so strong that unless the patient is very obese inability to feel it indicates a definite vascular lesion If coarctation of the aorta can be excluded and the patient's symptoms are not of sudden onset, then insidious thrombosis of the abdominal aorta is the most likely diagnosis Bilateral occlusion of the common or external iliac arteries will produce a similar clinical picture, but can be excluded either by aortography or by inspection of the vessels at operation

The other vascular disturbances are often minimal and have to be sought carefully Pallor of the feet when the patient is standing was noted in only one of our cases, but undue influence of gravity on the circulation to the feet as shown by marked pallor on elevation and either rubor or cyanosis on dependency was a constant finding in those cases in which it was looked for In the early stages the nutrition of the feet is good and it may remain so for many years Swelling of the limbs was noted in four patients but was probably not directly related to the aortic thrombosis In one (Case 6) it was undoubtedly due to œdema from cardiac failure, and in another (Case 10) early cardiac failure was suspected The third and fourth patients (Cases 8 and 9) had gross swelling of the lower limbs which was attributed to postural œdema For three months the third patient (Case 8) had been sitting in a chair both by day and by night Two of our cases had superficial gangrene, but in both local factors were responsible for the lesions Both Leriche (1946) and Martorell (1946) state that unless the patient dies from some other cause, gangrene of the feet eventually develops

The neurological disturbances can be attributed to the effects of the reduced blood supply upon the nerves and muscles of the lower limbs Wasting of the muscles is often difficult to detect since it is bilateral and symmetrical and therefore a normal limb is not available for comparison Fascicular twitching is often observed in the muscles of the lower limbs, not only in cases of aortic thrombosis, but in cases where the occlusion is in the popliteal or femoral artery The cause of this fasciculation is uncertain It is coarser than the true fibrillation seen in denervated muscles and resembles the coarse local tetanic fasciculation described by Denny-Brown and Pennybacker (1938) This occurs in fatigue and when there is excessive loss of sodium chloride, and it is closely related to muscle cramp A muscle fasciculus is a vascular and not a neurological unit, and it is therefore not altogether surprising that circulatory disturbances should lead to abnormal fascicular activity

Objective disturbances of sensation are the result of ischæmic neuropathy

An elevated blood pressure in the upper limbs has been noted in the majority of the reported cases It is uncertain whether this hypertension is to be regarded as part of the general cardiovascular disease which is present in most cases or whether it is a specific finding related to the aortic thrombosis Straus *et al* (1946) have attributed it to renal ischæmia as a result of occlusion of the renal arteries, but hypertension is present in many cases in which the thrombus has not extended as high as the renal arteries When first seen, one of our patients (Case 5) had a blood pressure of 120/70 mm Hg, but three weeks later it had risen to 200/110 mm Hg, in this case the renal arteries were not occluded

In most cases the occlusion can be attributed to arteriosclerosis Radiographs of the pelvis and thighs may show that there is calcification in the walls of the large arteries Our clinical and pathological studies lead us to the conclusion that in some cases thrombosis begins in the vessels of the lower limbs and extends slowly upwards (Cases 3 and 4), whereas in other cases the initial occlusion occurs in the iliac arteries or in the aorta itself In the latter group the main arteries distal to the block remain patent and could be refilled through collateral channels Although the clinical features suggest complete occlusion, in some cases aortography may show that the block is incomplete on one side This was noted in one of our cases (Case 8) and in two of the cases reported by Milanes *et al* (1950) The danger of an incomplete occlusion becoming complete is great, as is shown by the course of events in our Case 8 and by the appearance of the clot in Case 5 (Fig 18) When the occlusion of the aortic bifurcation is incomplete, portions of the thrombus may become detached and lodge in distal arteries, as happened in our Case 9

Although patients with aortic thrombosis may be severely disabled by intermittent claudication, in many cases the prognosis is surprisingly good both for life and for preservation of the lower limbs One of our patients has probably had the condition for eleven years, and other instances of long survival have been reported Death is due either to a sudden extension of the thrombus with involvement of the renal or mesenteric arteries, or to a cardiovascular catastrophe such as myocardial infarction

Two types of surgical treatment have been advocated resection of the aortic bifurcation combined with low lumbar sympathectomy (Leriche, 1940), and high bilateral lumbar sympathectomy (Leriche and Morel, 1948) We have no experience of the first of these methods, although a number of successful cases have been recorded It depends for its success upon early recognition of the condition, and a relatively healthy aorta and iliac arteries When performed in the early stages, high bilateral lumbar sympathectomy may improve the collateral circulation to the lower limbs In more advanced cases, even when done in two stages, this operation is not without risk because it may be followed by a rapid deterioration in the circulation in the ipsilateral limb, as happened in two of our cases Moreover, sympathectomy does nothing to minimise the danger of proximal extension of the thrombus If bilateral sympathectomy is performed, the approach should be transperitoneal, through a median incision, in order to conserve collateral arteries coursing between and in the muscles of the flanks

(TO BE CONCLUDED)

PLASMA FIBRINOGEN CONCENTRATION IN OCCLUSIVE ARTERIAL DISEASE

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AN increased plasma fibrinogen concentration has been reported in occlusive arterial disease In a series of 10 cases of thrombo-angiitis obliterans, Friedlander and Silbert (1931) found a mean concentration of 0 56 g per 100 ml plasma (g per cent) and in 29 cases (one febrile) Sposito *et al* (1947) found a mean concentration of 0 59 g per cent , which they regarded as a moderate increase above normal

A correlation with clinical features has not been reported

EXPERIMENTAL

The plasma fibrinogen concentration was determined in 32 male cases of obliterative arterial disease aged 24-66 years In each case the Wassermann reaction was negative , anticoagulants were not being given at the time of the determinations, although some patients may have been taking salicylates for the relief of pain The fibrinogen estimations were made as fibrin, either by the micro-Kjeldahl nitrogen method (6 cases) or by the dry weight of clot method (26 cases) Previous work had suggested that these methods gave equivalent results, and the " Student "-Fisher *t*-test showed an insignificant difference between the means of the two groups above ($0\ 1 < P < 0\ 2$)

For comparison with normal fibrinogen concentrations, 30 determinations by the second method were made on plasmas from male blood transfusion donors, presumed healthy, aged 19-48 years Further normal values were obtained from the literature

For comparison with high pathological values, determinations were made on 4 deeply jaundiced patients and on 6 patients with gross inflammatory lesions, none showing evidence of arterial disease, selected on the likelihood of finding very high fibrinogen concentrations (Gram, 1922 , Linton, 1932 , Ham and Curtis, 1938) These ten determinations also were made by the second method

RESULTS

(1) *Normal range* —The findings in the present normal series and the data obtained from the literature are shown comparatively in Table I

In each of the four series to which the test could be applied, the correlation between fibrinogen concentration and age was positive and in two it was significant, but it was verified that the magnitude of

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* In receipt of a grant from the Medical Research Council

the effect was negligible when compared to differences between the three main clinical groups studied

Two further estimates of the mean normal fibrinogen concentration (Friedlander and Silbert, 1931 , Sposito and Giannico, 1948) significantly higher than those shown in Table I, will be noted below

TABLE I

Plasma Fibrinogen Concentrations in Normal Males

Four published series and the present series

Source of Data	Number of Tests	Limits of Age in Years	Plasma Fibrinogen Concentration: Mean Concentration ±Standard Error where Known g per cent	Plasma Fibrinogen Concentration: Range of Concentration (Standard Deviation Parenthesised where Known) g per cent	Correlation with Age
Gram (1922)	25	19 69	0 27±0 01	0 20—0 36 (0 046)	Significant $r = +0\ 427$, $0\ 02 < P < 0\ 05$
Foster (1924)	23	3 63	0 34±0 01	0 26—0 45 (0 049)	Not significant $r = +0\ 100$ $0\ 6 < P < 0\ 7$
Greisheimer *et al* (1929) (i)	213	7 94	0 33±0 01	0 20—0 80 (0 084)	Significant $r = +0\ 460$, $P < 0\ 01$
Greisheimer *et al* (1929) (ii)	106	18 50	0 29±0 01	0 20—0 55	(Not given)
Ham and Curtis (1938)	19	25 61	0 25	0 19—0 33	" No outstanding " correlation
Present series	30	19 48	0 28±0 01	0 21—0 36 (0 039)	Not significant $r = +0\ 233$, $0\ 2 < P < 0\ 3$

The first series from Greisheimer *et al* includes the second Similar data are given by Lewinski (1903, quoted by Greisheimer *et al*), McLester (1922), Starlinger and Winands (1928 but mostly females), Burke and Weir (1933 but mostly from abnormals) and by Edsall *et al* (1944)

r = Correlation coefficient P = Probability of obtaining, by chance, a result more extreme than that observed

TABLE II

High Pathological Plasma Fibrinogen Concentrations

Clinical Condition	Number of Patients	Plasma Fibrinogen Concentration (g per cent): Mean ±S E	Plasma Fibrinogen Concentration (g per cent): Range
Deep jaundice	4	0 63±0 07	0 45—0 81
Gross inflammation	6	0 77±0 10	0 57—1 15

The mean concentrations of the two groups do not differ significantly
S E = Standard error of the mean

(2) *Inflammatory conditions and jaundice without arterial disease* — The data obtained from these patients is given in Table II It will be seen that the plasma fibrinogen concentrations found were of the order of twice to four times the mean normal concentration

(3) *Obliterative arterial disease.*—The results obtained in the cases of the present series are compared in Table III with the data given by Friedlander and Silbert (1931) and by Sposito *et al.* (1947). The age distribution of their cases is not given by Friedlander and Silbert, but is seen to be closely similar in the other two series: the difference is technically insignificant.

It might appear that the fibrinogen concentrations in the cases described by the American and by the Italian workers were considerably higher than in the three cases of the present series, but it is seen from Table III that their mean normal values are also higher than the mean value obtained from the present normal series. Expressed as percentages of their respective normal values, the mean pathological values of the three series become:—Friedlander and Silbert, 130 per cent.; Sposito *et al.*, 147 per cent.; present series, 131 per cent. The difference between the raw mean values of the two reported series is technically insignificant; it is perhaps hardly justifiable to make a more precise comparison between these values and the corresponding mean value of the present series, than that given above: in relation to their respective mean normal values, the three groups of pathological data appear comparable.

TABLE III

Plasma Fibrinogen Concentrations in Occlusive Arterial Disease

The findings of Friedlander and Silbert (1931) and of Sposito *et al.* (1947) compared with those of the present series

Series	Number of Patients	Pathological Material				Mean Normal Plasma Fibrinogen Concentration Given as (g. per cent.)
		Age Distribution of Patients (years)		Plasma Fibrinogen Concentration (g. per cent.)		
		Mean ± S.E.	S.D.	Mean ± S.E.	S.D.	
Friedlander and Silbert (1931)	10			0.56 ± 0.029	0.09	0.43 (mean of single determinations in four persons)
Sposito *et al.* (1947)	29	40.7 ± 1.8	9.5	0.590 ± 0.022	0.118	0.4 (Sposito and Giannico, 1948: derivation not given)
Present series	32	42.4 ± 1.6	9.3	0.368 ± 0.017	0.099	0.28 ± 0.01 (Table I)

S.E. = Standard error of the mean S.D. = Standard deviation

Correlation with clinical characteristics

The fibrinogen concentrations found in the present series were studied in relation to various clinical features.

(1) *Incidence of migratory phlebitis* (Table IV).—Five patients showed active migratory phlebitis at the time of the determination; 4 others were known to have had the condition in the past but were

quiescent in this respect when tested, the remaining 23 were without known migratory phlebitis at any time Taking the mean ages of the groups, the 5 patients with active phlebitis were significantly younger than the 23 patients never known to have had the condition, the 4 with quiescent phlebitis were of intermediate age Despite this clear distinction between the first and the third groups (corresponding to a clinical differentiation of thrombo-angiitis obliterans from arterio-sclerotic arterial occlusion), the mean plasma fibrinogen concentrations of these two groups did not differ significantly

(2) *Duration of arterial occlusion when tested*—At the time of the determination, there was evidence in all cases of established arterial insufficiency, although in 2 the clinical picture also suggested that a further spread of the arterial lesion had recently occurred One man, aged 44 years, who had suffered from intermittent claudication in the left leg but without impairment of the nutrition of the skin, suddenly developed pain in the same leg and noticed pallor in the foot tested eleven days after this event, his plasma fibrinogen concentration was found to be 0 62 g per cent The leg required amputation three weeks later The other man, a Pole aged 24 years, developed ulceration of the great toe of the affected leg, ten to twelve days after the onset his plasma fibrinogen concentration was found to be 0 47 g per cent

TABLE IV

Plasma Fibrinogen Concentrations in Occlusive Arterial Disease

Classification by incidence of migratory phlebitis

Incidence of Migratory Phlebitis	Number of Patients	Age (years)		Plasma Fibrinogen Concentration (g per cent)	
		Mean±S E	S D	Mean±S E	S D
Active when tested	5	36 2±2 8	6 3	0 330±0 031	0 069
Previously active but quiescent when tested	4	40 5±2 0	4 0	0 388±0 021	0 041
Without known phlebitis	23	42 7±2 1	10 1	0 373±0 023	0 111

The difference between the mean ages of the first and third groups is significant (0 01 < P < 0 02)

S E = Standard error of the mean

S D = Standard deviation

P = Probability of obtaining, by chance, a result more extreme than that observed

(3) *Incidence of gangrene*—Gangrene was known to have been present at the time of the determination in 3 patients in whom the plasma fibrinogen concentrations were found to be 0 22, 0 47 and 0 71 g per cent The second case is that mentioned above, in the third case the lesion was infected this concentration was the highest recorded in the series

(4) *Incidence of other inflammatory lesions*—In addition to the

patient with infected gangrene, minor inflammatory lesions were found in 3 patients at the time that the determination was made. the plasma fibrinogen concentrations were 0.37, 0.39 and 0.43 g. per cent.

(5) *Incidence of epidermophytosis pedis.*—Fungus infection of the feet has been thought important in the natural history of arterial occlusion. At the time of the determination, clinical evidence of epidermophytosis pedis was present in 4 patients. The plasma fibrinogen concentrations were 0.22, 0.34, 0.34 and 0.62 g. per cent., the fourth case being that described in Section (2) above.

Thus, the two highest fibrinogen values in the series, 0.71 and 0.62 g. per cent., occurred respectively in a case with infected gangrene and in a case with gross impairment of tissue nutrition; also, a patient with a gangrenous ulcer gave a value of 0.47 g. per cent. With one exception (0.48 g. per cent. in a man of 62 years) no other case in the series presented a fibrinogen concentration above 0.44 g. per cent.

DISCUSSION

(1) *Normal range of fibrinogen concentration.*—It appears that the mean normal plasma fibrinogen concentration rises slightly with age, but it has not been found necessary in the present work to consider age differences when comparing the fibrinogen concentrations of the three main clinical groups.

The normal fibrinogen concentrations given by Friedlander and Silbert (1931) and by Sposito and Giannico (1948) are considerably above the other values studied in Table I. The difference may be observational rather than physiological but in any case somewhat obscures the interpretation of pathological data. Elsewhere, the latter authors (Sposito and Giannico, 1944) ascribe their fibrinogen determination to M. Lassier, who obtained the dry weight of fibrin formed by the spontaneous clotting of native plasma centrifuged in the cold (described by Lian and Frumusan, 1938, who gave the normal range by this method as slightly above 0.4-0.5 g. per cent.).

(2) *Fibrinogen concentration in occlusive arterial disease.*—From a comparison with the normal and with the grossly pathological ranges of the present series, it is clear that the range of fibrinogen concentration found in the cases of arterial occlusion is moderately increased above normal (confirming the finding of Sposito *et al.*, 1947, in relation to their own normal value).

The relation of plasma fibrinogen concentration to clinical features

Analysis of the cases of the present series according to the incidence of phlebitis, gangrene, minor inflammatory lesions or of epidermophytosis pedis fails to demonstrate a simple relationship between the plasma fibrinogen concentration and any of these features. It is seen that three of the four highest fibrinogen concentrations recorded were associated with overt inflammatory states Although 2 of these patients are thought to have suffered a recent exacerbation of their arterial lesions, it seems likely that their high fibrinogen concentrations were an indirect result rather than the cause of the process

By an extension of this argument, the other evidence presented suggests that the less markedly raised fibrinogen concentrations found in the majority of cases in this series represent milder inflammatory reactions to the disease process This is in line with the well-known response of the plasma fibrinogen concentration to inflammatory states in general (Gram, 1922 , Foster, 1924 , etc) It is thus not necessary to postulate that a high plasma fibrinogen concentration predisposes to thrombosis This accords with the findings of Meyers (1948) in 28 cases of coronary infarction and with the recently-expressed view of Quick (1951)

SUMMARY

Plasma fibrinogen concentrations have been determined in 32 cases of occlusive arterial disease, including 9 cases with, or having had, migratory phlebitis Comparison with concentrations in normal individuals and in patients with gross inflammatory lesions and with jaundice showed the concentrations found in the arterial occlusion group to represent a moderate increase over normal The increase was not found to be specifically related to thrombotic manifestations but was thought to represent a non-specific inflammatory reaction

It is a pleasure to acknowledge my indebtedness to Dr C C Burt for the provision of clinical data, to Dr R A Cumming, Regional Director of the South East Scotland Regional Blood Transfusion Service, for the provision of normal blood samples and to Dr P Armitage of the Medical Research Council Statistical Research Unit, London School of Hygiene, in the analysis of the numerical data

REFERENCES

BURKE, C F , and WEIR, J F (1933), *Journ Lab Clin Med* , 18, 657
EDSALL, J T , FERRY, R M , and ARMSTRONG, S H (1944), *Journ Clin Invest* , 23, 557
FOSTER, D P (1924), *Arch Intern Med* , 34, 301
FRIEDLANDER, M , and SILBERT, S (1931), *Arch Intern Med* , 48, 500
GRAM, H C (1922), *Acta med Scand* , 56, 107
GREISHEIMER E M , JOHNSON, O H and RYAN, M (1929), *Amer Journ Med Sci* , 177, 816
HAM, T H , and CURTIS, F C (1938), *Medicine, Baltimore*, 17, 413
LIAN, C , and FRUMUSAN, P (1938), *Presse med* , 46, 369
LINTON, R R (1932), *Ann Surg* , 96, 394
MCLESTER, J S (1922), *Journ Amer Med Assoc* , 79, 17
MEYERS, L (1948), *Arch Intern Med* , 82, 419
QUICK, A J (1951), *The Physiology and Pathology of Hemostasis*, p 158 London Henry Kimpton
SPOSITO, M , and GIANNICO, O (1944) *Giorn clin Med* 25, 1
SPOSITO, M , and GIANNICO, O (1948), *Progr Med* , *Napoli* 4, 74
SPOSITO, M , GIANNICO, O , and MARRAZZA, P (1947), *Policlinico* 54 1235
STARLINGER W , and WINANDS, E (1928), *Z ges exp Med* , 60 138

A STUDY OF 200 CASES OF APPENDICITIS WITH SPECIAL REFERENCE TO THEIR BACTERIOLOGY

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DURING a period of thirty-three months—from July 1948 to March 1951, 1172 appendicectomies were performed at Peel Hospital At one period in late 1949 and early 1950 there was a considerable increase in the average number of cases of acute appendicitis, many of which were gangrenous, so that we wondered whether there could be any specific micro-organism acting as the causal agent in what appeared to be a minor epidemic In view of this, a bacteriological investigation was carried out on 200 appendices, the majority of which were acutely inflamed

CLINICAL

Table I gives the age and sex incidence of the 200 cases examined.

TABLE I

	0 10	11 20	21 30	31 40	41 50	51 60	61 70	71 80	Over 80	Total
Males	4	30	24	15	11	7	1	2		94
Females	4	35	28	15	10	10	2	1	1	106
Total	8	65	52	30	21	17	3	3	1	200

Many writers in the past have investigated the sex-ratio and have come to the conclusion that appendicitis is more frequent among males than females Moloney *et al* (1950) found that there were 591 males and 483 females admitted with true appendicitis to the Radcliffe Infirmary, Oxford, during the four years 1945-48 Our figures, limited to the 200 cases under bacteriological review show a reversal of the usual findings in this respect Table I shows that appendicitis is essentially a disease of people under 50 years, the average age being 28 years In 41 per cent of cases it was the first attack of abdominal pain from which the patient had suffered Of the 24 patients over 50 in only 7 was this the first attack of pain with which they were admitted In 73 5 per cent there had been nausea and/or vomiting On arrival in hospital the temperature was elevated in 19 per cent of cases and the pulse rate was increased in 19 5 per cent of cases These last two findings illustrate how temperature and pulse rate are not often helpful in the early diagnosis of acute appendicitis In the majority of cases the history and clinical examination findings as far as routine textbook descriptions are concerned were atypical These "atypical" histories and findings may well be in part the result of the position in which the appendix was found at operation

During the period of thirty-three months there were 6 deaths following appendicectomy from the following causes General peritonitis (2) aged 14 and 24, paralytic ileus (2) aged 45 and 50, multiple liver abcesses (1) aged 41, general debility (1) aged 68 (died five days after operation) It should be noted from the ages of these 6 patients that none of them had attained their three score years and ten

TABLE II

Organisms Present in	No Organisms Found	Pus Present in	Gangrenous	No Pus or Exudate	Normal
97 per cent	3 per cent	57 per cent	20 5 per cent	8 5 per cent	14 per cent

TABLE III

Frequency of Particular Bacterial Groups or Species from Diseased Appendices

Organisms	Times Isolated (per cent)	Alone (per cent)	Predominant (per cent)	Isolated Wall (per cent)	From Contents (per cent)
Coliform bacilli	96	21	82	65	68
Strept fæcalis	46	0 5	3	36	38
Lactobacillus acidophilus	27			23	24
Alkaligenes fæcalis	1			1	1
Clostridium perfringens	11			4	9
Other clostridia	8			4	8
Bacteroides	10		0 5	8	9
Strept anærobius	4			2	2
Proteus vulgaris	2			1	1
Pseudomonas æruginosa	2		1	1	1
Micrococcus pyogenes albus (c—)	14			11	10
Micrococcus pyogenes albus (c+)	1			1	
Micrococcus pyogenes aureus (c—)	1			1	1
Micrococcus pyogenes aureus (c+)	2		1	2	2
Strept mitis	2			2	2
Diplococcus pneumoniæ Type 1	0 5			0 5	0 5
Diplococcus pneumoniæ Type 19	0 5				0 5
Diplococcus pneumoniæ Type 23	0 5	0 5	0 5	0 5	0 5
Hæmophilus influenzæ	0 5			0 5	0 5
Diphtheroids	3			3	2

c = coagulase

BACTERIOLOGICAL EXAMINATION

The appendix was removed from its container with sterile forceps and placed in a sterile tray Using sterile instruments the appendix was opened in its entire length to expose the mucous membrane

Specimens were taken (1) from the contents (fæces, pus, etc) if present, and (2) the inner wall of the appendix (after pus, fæces, etc , had been thoroughly removed) by scarifying the mucous membrane and penetrating into the submucosa with a sharp instrument The following media were inoculated —blood agar, glucose blood agar, MacConkey's, and cooked meat medium (bullock's heart) Both ærobic and anærobic methods of cultivation were employed Film preparations were also made from the contents and wall, and stained by Gram's method in order to study the exudate

After incubation at 37° C for twenty-four, forty-eight, and in some cases seventy-two hours, the inoculated media were examined The results are shown in Tables II, III and IV

TABLE IV

Species Isolated from the 28 Normal Appendices
(22 *Contained Organisms*)

	Times Isolated	Alone	Predominant	Wall	Contents
Coliform bacilli	22	5	15	12	12
Strept fæcalis	9			7	7
Lactobacillus acidophilus	5			5	4
Clostridium perfringens	2			1	2
Other clostridia	3			2	1
Streptococcus anærobius	1			1	1
Micrococcus pyogenes albus (c—)	4	1	1	3	3
Strept mitis	2			1	1

DISCUSSION

The most important causative factors in the ætiology of acute appendicitis are obstruction of the appendicular lumen and infection (Boyd)

While it is possible for obstruction *per se* to cause appendicular disease, the presence of bacteria in an otherwise normal appendix may not by itself give rise to appendicitis Wilkie (1931) emphasised the importance of obstruction and not inflammation in fatal cases of appendicular diseases, and he stressed the danger of a sudden and complete obstruction of the appendix containing fæcal matter which could lead to tension gangrene from pressure, followed by perforation. In this type of case, by no means rare, it would not seem likely that any bacteria present would have time to play a major part in the morbid process Wagenstein and Dennis (1939) maintained that the obstructed and exteriorised human appendix could develop a secretory pressure almost equal to systolic blood pressure

It was shown by Wells (1947) in experimental work in rabbits, that intravenous injection or the introduction into the appendix of such organisms as non-hæmolytic streptococci, anærobic bacilli from human inflamed appendices, emulsion of purulent contents of human appendices, or hæmolytic streptococci from the throats of cases of tonsillitis, all failed to produce acute appendicitis Wells stressed the importance of preliminary damage to the mucous membrane as being a factor in the production of acute appendicitis Obstruction of the lumen with a damaged mucous membrane was always followed by acute inflammation and death of the animal—the damage to the mucous membrane may be quite trivial Nigam (1947) also demonstrated in experimental work how intravenous or intraluminal injections of virulent streptococci sometimes failed to cause any gross or even microscopical lesion in the appendix

What role then do bacteria play in the ætiology of acute appendicitis? Many different species of bacteria can be found both in the healthy and diseased appendix This is well illustrated in the results of the present investigation The important points for discussion in this respect are (1) the origin of these micro-organisms, and (2) the pathogenicity of the various species Three main views have been put forward regarding the origin of infection in appendicitis, (1) enterogenous (Weinberg *et al*, 1928), (2) intrinsic (Aschoff, 1931), while (3) Poynton and Paine (1911), Rosenoff (1916) and Wakeley and Childs (1950) favour the hæmatogenous route Rosenow stresses the possibility of a focus of infection of streptococci in the teeth or tonsil, the organisms developing a selective affinity for the appendix It was, however, pointed out by Aschoff in 1931 that the principal organisms present in the tonsil and appendix both in health and disease are different—hæmolytic streptococci being found in the tonsil and non-hæmolytic streptococci (*Strept fæcalis*) in the appendix Again, it is observed that most attacks of acute appendicitis are unconnected with any preceding illness, nor is there a rise in cases of appendicitis in conditions of septicæmia or during such epidemics as acute tonsillitis In the present series only one case had a history of recent tonsillitis Moreover, Bowen (1943) did not find any suggestion of an epidemic character in his statistical survey of appendicitis

This investigation has shown the large variety of bacterial species that can be found in the appendix It also illustrates that the majority of species found in both the diseased and healthy appendix are those which are found as commensals in the healthy intestinal tract It would appear that the following organisms might be able to cause appendicitis, viz coliform bacilli, *Strept fæcalis*, bacteroides group, pneumococcus, *Ps æruginosa* and *M pyogenes aureus*—these organisms being found alone or as the predominant species in diseased appendices However, primary place must be given to the coliform bacilli for the following reasons —(1) they were found alone in 21 per cent cases, (2) predominant organisms in 82 per cent cases, (3) found alone in 11 per cent purulent cases, (4) only 3 of the 113 appendices containing pus did not contain coliform bacilli, (5) coliform bacilli were present in all gangrenous cases and found alone in 3 per cent of such cases, (6) in 4 cases of appendix abscesses coliform bacilli were present in all 4 and were predominant in 2

The next most frequent species isolated was *Strept fæcalis* This organism was isolated alone in 0 5 per cent cases and was the predominant species in 3 per cent It is possible that it may play an important role in initiating a pathological condition in the appendix, but only in a very small percentage of cases Aschoff (1931) stressed the importance of *Strept fæcalis* as being a causal agent in appendicitis and he maintained there were increased numbers of this organism in the distal part of the organ We, however, believe that coliform bacilli are more important in initiating the morbid process—a view also held by Weinberg *et al* (1928) who showed how a few *Esch coli* could greatly increase the virulence of *Strept fæcalis* Our findings are similar to those of Weinberg *et al* in that the most frequent combination was *E coli* and *Strept fæcalis* alone, or in association with other organisms *Proteus* and *Ps aeruginosa* can be found in the intestine and occasionally may give rise to pathological conditions In this investigation they did not play a dominant role in the infection

As regards the anærobic bacteria it does not appear that any of these by themselves can cause appendicitis, only one species—a *Spherophorus necrophorus*-like organism Bacteroides group—being found predominant and in only 0 5 per cent cases, and none being found alone There is no doubt they play a great part in furthering the pathological process, once begun All the anærobic species isolated in this investigation can be found in the normal bowel Some, such as *Spherophorus necrophorus* and *Bacteroides fragilis* are definitely associated with gangrenous and suppurative conditions in certain parts of the body, but it is not known whether they are the primary ætiological agents In the conditions of appendicitis it appears they are not the primary agents, but require the presence of other species to initiate the process or perhaps to increase their virulence. Matt (1950) obtained a pure growth of *Spherophorus necrophorus* from an intra-abdominal abscess in a case of acute segmental ileitis. Dack *et al* (1937) found *Spherophorus necrophorus* the predominant anærobic organism in 3 out of 4 cases of chronic ulcerative colitis. Anærobes in the present investigation were found in 30 per cent. gangrenous and in 20 per cent non-gangrenous cases The commonest anærobe isolated was *Cl perfringens* This was also the experience of Weinberg *et al*, and they showed how *Esch coli* could increase the virulence of *Cl perfringens*

It appears that the normal intestinal commensals take on a pathogenic role under certain circumstances How they do this is not clear. It may be that such factors as stagnation of contents, or appendicular secretion, or the presence of other bacterial species may increase their virulence, *i e* a symbiotic virulence enhancement We believe that coliform bacilli are the primary cause of the inflammation in the majority of cases Such conditions as obstruction with its accompanying increased intra-luminal pressure and stagnation of contents would cause devitilisation of the mucous membrane leading to loss of equilibrium between virulence of the organism and resistance on the part of the mucous membrane, resulting in a state of affairs favourable to the organism According to Dennis (1941) inflamed appendices present an average resistance to outflow three times normal One must not regard virulence as some specific intrinsic quality of the particular species, but rather the summation of factors both on the part of the organism and host which results in a condition more favourable to the bacteria

Bohning (1931) suggests that any disturbance in the self-cleansing of the secretions of the appendix will lead to increase in virulence, and she maintains that the bacterial flora of the appendix during digestion and starvation are different, and it also changes in various diseases which hinders the development of appendicitis

Staphylococci can be found in normal fæces On routine media, however, they tend to be overgrown by *Esch coli* This can be overcome by using a selective medium

It is not usual to find pneumococci in the normal intestine, as the presence of bile would be inhibitory In one case, however, *Pneumococcus* type 23 was isolated alone both from the wall of the appendix and the contents, and one can only assume that this organism played a major part in the inflammatory reaction which was of the chronic type The question arises by what route the pneumococcus reaches the appendix from its initial locus in the upper respiratory passages This organism is not likely to reach the appendix via the stomach and small intestine a hæmatogenous origin of the infection seems more likely

The isolation of a hæmophilic organism (*Hæm influenzæ*), although not the predominant organism in the particular case, was interesting, in that we can find no previous record of a hæmophilic species having been isolated from the appendix This type of organism normally inhabits the upper respiratory tract The same question arises in this case as in the case of the pneumococcus

The infection in appendicitis, therefore, appears to be endogenous in origin We believe that anatomical and/or physiological damage to the mucous membrane is an important factor, and in conjunction with stagnation of contents and appendicular secretion will be favourable to the bacteria present It is easy to imagine how the mucous membrane is subject to repeated trauma on account of the mobility of the appendix particularly when associated with bands or adhesions, and also on account of the easy access of intestinal contents which must return to the bowel via the same route We believe that the intestinal organisms gain access to the wall of the appendix from the lumen, through either an anatomical breach or a physiologically devitalised part of the mucosa, and that these changes in the mucosa are primarily brought about by the obstructing agent—fæcolith, foreign body, adhesions, threadworms, spasm, kink, etc , and pressure distension distal to the obstruction This weakened mucous membrane allows any organisms present to establish themselves and by taking advantage of this abnormal state produce their effects Appendicitis affords an example of a condition caused by organisms which in one part of the body are pathogenic, yet in another are quite harmless

Neither *Ent histolytica* nor *Actinomyces* was isolated from any specimen The absence of these organisms is in part responsible for the fact that there was no case in this series in which fæcal fistula developed post-operatively In contrast to Raftery, Trafas and McClure (1950) who found *Histoplasma capsulatum* in 5 per cent of 2, 135 appendices, this organism was not found in any of our cases

The findings in this investigation do not show that this special prevalence of appendicitis was due to any particular species of micro-organism Whether there was some as yet unknown specific factor responsible for damaging the mucous membrane of the appendix other than an obstructing agent is not known

Aschoff believes that most people suffer from one or more attacks of acute appendicitis during life, and although the appendix may not appear abnormal by macroscopic and routine microscopic examination, nevertheless, by the employment of special methods it often shows signs of inflammation

In 1889 Charles McBurney wrote —" What we wish to accomplish in the treatment of appendicitis is not to save half of our cases, not four cases out of five, but all of them " After sixty-two years of very considerable progress, this aim has not yet been accomplished, and it is our opinion, that early surgery combined if necessary with chemotherapy is the only way to attain this objective, as we are unable to deal with the appendicular obstruction other than by operation and the organisms responsible are already in the lumen waiting their chance to cause appendicitis We agree with Boyce (1951), Schullinger (1950) and many others that there is no place for the treatment of acute appendicitis with chemotherapy without operation, as this will not stop the disease from progressing, and will often mask the development of complications Perhaps Moloney, Russell and Wilson (1950) are theoretically correct when they asked whether " the safety of appendicectomy had not in some measure hampered the growth of clinical judgment," but as long as there are many deaths annually (152 in Scotland in 1950 and 1252 in England and Wales in 1949) and so long as appendicitis tends to present itself in " atypical " forms and often mimic other abdominal diseases, and so long as early appendicectomy is associated with virtually no mortality, we consider this to be the only justifiable treatment where there are reasonable grounds for the diagnosis of acute appendicitis

SUMMARY

1 Some of the important clinical and operative features are given in 200 cases of appendicitis, the appendices of which were examined bacteriologically

2 Bacteriological examination revealed that the commensals of the bowel were present in the wall of the appendix in cases of appendicitis Coliform bacilli were the predominant organisms

3 From 28 normal appendices intestinal commensal bacteria were isolated in 22 cases The flora from the wall and contents showed no appreciable difference

4 It is our opinion that the bacteria gained access to the wall of the appendix through a breach in a devitalised portion of the appendicular mucosa

5 Early surgery combined, if required, with chemotherapy is the treatment of choice in acute appendicitis

We express our thanks to Mr Quarry Wood for his advice and interest in this investigation, and to Dr Levinthal for his typing of the pneumococci

REFERENCES

ASCHOFF, L (1931), *Münd Med Woch*, 78, 1419

ASCHOFF, L (1931), *Beitrage zur Path Anat Ziegler*, 87, 481

BOHNING, F (1931), *Beitrage zur Path Anat Ziegler*, 87, 611

BOWEN, W H (1943), *Brit Journ Surg*, 31, 127.

BOYCE, F F (1951), *Ann Surg*, 133, No 3, 428, March

BOYD (1938), *Textbook of Pathology*, 3rd edition London

DACK, G M, DRAGSTEDT, L R, and HEINZ, T E (1937), *Journ Inf Dis*, 60, 335

DENNIS (1941), *Arch Surg*, 43, 1021

MATT, J G (1950), *Ann Surg*, 131, No 2, 277

MCBURNEY, C (1889), *New York Med Journ*, 50, 679

MOLONEY, G E, RUSSELL, W J, and WILSON, D C (1950), *Brit Journ Surg*, July, 38, 52

NIGAM, R (1947), *Indian Med Gazette*, 82, 709

POYNTON, F J, and PAINE, A (1911), *Proc Roy Soc Med*, 5, 18, Part iii

RAFTERY, A, TRAFAS, P C, and MCCLURE, R D (1950), *Ann Surg*, 132, 720, October

ROSENOW, E C (1916) *Journ Inf Dis*, 16, 240

SCHULLINGER, R N (1950), *Surgery Clinics N America*, 30, 495

WAGENSTEIN, O H, and DENNIS, C (1939), *Ann Surg*, 110, 629

WAKELY and CHILDS (1950), *Brit Med Journ* 16th December, p 1347

WELLS, A Q (1947), *Brit Journ Surg*, 24, 766

WEINBERG, M, PREVOT, A R, DAVESNE, J, and RENARD, C (1928), *Ann Inst Pasteur*, 42, 1167

WILKIE, D P D (1931), *Brit Med Journ*, 1, 253

NOTES

University of Edinburgh

At a Graduation Ceremonial held in the Upper Library on Friday, 14th December 1951, the following degrees were conferred —

The Degree of Doctor of Medicine —Percy Francis de Caires, British Guiana, M P M, M B, CH B, 1938 (*In absentiâ*), Robert McKenzie Fulton, Scotland, M B, CH B (with Honours), 1942 (*Highly Commended for Thesis*), Christopher Eberhard Ludwig Haffner, England, M B, CH B, 1944 (*In absentiâ*), Thomas Harrison, England, M B, CH B, 1921 (*In absentiâ*), Harry Oswald-Smith, Scotland, M B, CH B, 1900, Alistair Sutherland Livingston Rae, Scotland, M B, CH B, 1935, Alan Robert Somner, Scotland, M B, CH B, 1946 (*Highly Commended for Thesis*)

The Degree of Doctor of Philosophy—In the Faculty of Medicine —Deb Prasanna Basu, M B, B S (CALCUTTA), Aubrey Stanislaus Outschoorn, M B, L M S (CEYLON)

The Degrees of Bachelor of Medicine and Bachelor of Surgery —Audrey Nora Henderson Andrew (*nee* Robertson), Scotland, William Robert Cameron Andrew, Scotland, Eric Sutton Blackadder, Scotland, Frank Keppie Paterson Brydon, Scotland, Robert Christie Buchanan, Scotland, Isobel Catherine Campbell, Scotland, George Malcolm Dewar, Scotland, Johannes Marthinus Petrus Dippenaar, South Africa, William Fyffe Morrison Dorward, M A, Scotland, Margaret Joyce Field, B SC, PH D England (*In absentiâ*), Peter Traill Fraser, Scotland, Paul William Eardley Hayward, England, Roman Stanislaw Jarema, Poland, John Harold Jennings, England, Donald Ferguson Kerr, Scotland, Margaret Livingstone Liddell, Scotland, Douglas Watson Lyon, Scotland, Mary Iona McArthur, Scotland, Ranald Macdonald, England, Malcolm Alexander McFadyen, Scotland, Dennis Wenceslas Maxa, Scotland, Alexander Edwin Meek, Scotland, Charles Cameron Moir, Scotland, George Dimond Earngey Morris, Scotland, Johan Ekhard Munro, South Africa, Alexander Euan Mackay Reekie, Scotland, William Douglas Riddell, Scotland, Adam Alan Robertson, Scotland, Albert Henry Ian Scott, Scotland, William Allan Simpson, Scotland, Robert More Stewart, Scotland, John Hugh Sutherland, Scotland, George Peter Syme-Thomson, England, John Millar Tainsh, Scotland, Jean Caverhill Taylor, Scotland, Charles Graeme Marshall Third, Scotland, Frederick Augustus Viapree, Scotland, Frederic Eustace Berkeley Wills, British Guiana

Diploma in Medical Radiodiagnosis —Alan Lien-yiu Chen, M B (WEST CHINA UNION), James MacGregor McKay, M B, CH B (ABERD), Mihir Kumar Mitter, M B (CALCUTTA)

Diploma in Medical Radiotherapy —Walter Disney Rider, M B, CH B

Sister-Tutor Certificate —Ellen Mona Haigh, Margaret Mary Hannon, Bertha May Hawkins, Ena Isobel Leiper, Anne McSharry, Sarah Matthew, John Kendrick Minks, Winifred Catherine MacIldowie Potter

The Vans Dunlop Scholarship in Forensic Medicine and Obstetrics —John Patrick Laidlaw

The Llewellyn Bevan Prize —James Farquhar Ogilvie Mitchell, M D

The Goldie Prizes for Dental Mechanics —First Prize—Ronald James Gutteridge , Second Prize—Eric Arthur Binnie Gibson

The Tindal Scholarship —Robert Burrows, B SC , M R C V S

Royal College of Surgeons of Edinburgh

AT a meeting of the Royal College of Surgeons of Edinburgh held on 19th December 1951, Professor Walter Mercer, President in the Chair, the following who passed the requisite examinations were admitted Fellows —Thomas Laird Barclay, M B , CH B , UNIV EDIN 1947 , Francis Bauer, M D , UNIV PRAGUE 1938, L R C S EDIN 1948 , Lydia Colaco, M B , B S , UNIV MADRAS 1942 , Joseph Kevin Craig, M B , CH B , UNIV MANCH 1946 , Hugh Arnold Freeman Dudley, M B , CH B , UNIV EDIN 1947 , Alan Stoddart Lambert, M B , CH B , UNIV NEW ZEAL 1946 , Daniel Gerard Lane, M B , B S , UNIV QUEENSLAND, AUSTRALIA 1947 , Francis Douglas Martinson, M B , CH B , UNIV EDIN 1942 , Shreemohan Mishra, M B , B S , UNIV PATNA 1947 , Archibald Hope McCallum, M B , CH B , UNIV CAPE TOWN 1945 , John Andrew McCredie, M B , B CH , B A O , QUEEN'S UNIV BELFAST 1946 , Ian Grant Mackenzie, M B , CH B , UNIV EDIN 1946, M D 1948 , Satya Nand, M B , B S , UNIV PUNJAB 1948 , William Harford Rutherford, M B , B CH , TRINITY COLL DUBLIN 1944 , Leo Stein, M B , CH B , UNIV WITWATERSRAND 1943 , Daniel Pieter Viljoen, M R C S ENG , L R C P LOND 1932 , James Alfred Scott Wilson, M D , C M , DALHOUSIE UNIV CANADA 1948

Fellows in Dental Surgery —Professor Robert Humphrey McKeag, M A , M B , B CH , B A O , B DENT SC , Department of Dental Surgery, University of Ceylon was elected a Fellow in Dental Surgery without examination , and John Stevenson Howie, B D S , UNIV NEW ZEAL was elected a Fellow after examination

NEW BOOKS

Electron Microscopic Histology of the Heart By BRUNO KISCH, M D Pp vi+106 illustrated New York Brooklyn Medical Press 1951 Price $5 00

The author, using sections between 0 1 and 0 2 μ in thickness, has studied the finer structure of the heart His findings are beautifully shown by microphotographs of the tissues This difficult and detailed work may open up a fuller understanding of the muscle of the heart and of the action of drugs on it

A Text-Book of Medicine Edited by E NOBLE CHAMBERLAIN, M D , M SC , F R C P Pp xii+962 Bristol John Wright & Sons 1951 Price 50s

It is most fitting that Noble Chamberlain has now produced a text-book of medicine forming a companion volume to his well known *Symptoms and Signs* Those who know his previous work will enjoy in his latest book the clarity of description which, if at times dogmatic, allows easy reading and understanding for the undergraduate Each disease is described under ætiology, pathology, clinical findings, diagnosis and treatment The last in many cases is brief and, with such rapid progress in therapeutics, it is felt that an additional chapter on the antiobiotics would have been of great service, especially to the general practitioner

It is generally held that American publications are all round better productions than the British counterpart in regard to text and illustrations It is refreshing and heartening to see that in this book such an opinion is completely refuted

Venereal Diseases Described for Nurses By R C L BATCHELOR, M A, M B, CH B, F R C S ED, M R C P E, D P H, and MARJORIE MURRELL, M B, B S, M R C S, F R C S ED, D P H Pp xii+217, with 43 figures Edinburgh E & S Livingstone 1951 Price 12s 6d net

This excellent small volume, although intended for the nursing profession, does itself an injustice by using the latter qualification in its title page Its concise and well-illustrated text describes the onset, progress, commonly associated diseases and the more conservative methods of treatment Over all it produces a masterly and composite picture which the student, practitioner or postgraduate, with limited reading time, will not find in any other textbook of Venereology

The Electrical Activity of the Nervous System By MARY A B BRAZIER, B SC PH D Pp 220, with 96 illustrations London Pitman 1951 Price 25s net

Although this book is entitled a Textbook for Students, it contains far more than a medical student can be expected to cover It is neither accurate nor critical enough for students in a Final Honours Course in Physiology, but students for higher degrees which require a knowledge of neurophysiology may find the chapters on the ear and the eye useful The chapters on the cortex and electroencephalogram contain a useful guide to the recent literature which is as yet incompletely dealt with in standard textbooks

The Mode of Action of Anæsthetics By T A B HARRIS, M B, B S, D A, F F A Pp xii+768, with 22 figures Edinburgh Livingstone 1951 Price 42s net

The reviewer considers that in many respects this book on anæsthesia may be regarded as one of the best ever published In it the author has crystallised the fruits of years of painstaking research of the literature of basic and clinical medical science The chemistry and pharmacology of the many agents employed in anæsthesia are explained in detail rarely seen except in special journals A working hypothesis of the mode of action of anæsthetics is presented and forms a reasonably credible basis for the clinical section of the book Although the style is frequently repetitive this appears to be purposely designed as a mode of emphasis This volume will be of the highest value to students and teachers and will help both to a better understanding and appreciation of the complex scientific aspects of a subject which until recent years many have been content to regard as merely an art

Law relating to Hospitals and Kindred Institutions Supplement to 1949 (Second) Edition By S R SPELLER, LL B Pp viii+87 London H K Lewis 1951 Price 12s 6d net

This publication has no separate existence as a book but is merely to bring the second edition up to date It is supplementary to the parent volume A number of new subjects have been introduced, including the licensing of official motor cars, cinematographs in hospitals and area Nurse-training committees The subject-matter deals only with English Law

Bronchial Asthma—Its Relation to Upper Respiratory Tract Infection By R J WHITEMAN, M B, CH B, F R A C S Pp xi+184 London H K Lewis 1951 Price 15s net

The work described in this book is entirely clinical It is the experience of the author dealing with many cases of chronic nasal infection The purpose of this volume is threefold firstly an attempt to bring evidence to show that chronic nasal catarrh is the result of inadequately treated acute coryza, secondly it outlines both hospital and home treatment for nasal catarrh, especially in children, thirdly it shows the application of this treatment to patients suffering from hay fever and asthma

Asthma is a highly controversial subject The author avoids entering into any controversy but merely shows the improvement in asthmatics when their upper respiratory tract infection is adequately treated

Diseases of the Endocrine Glands By LOUIS J SOFFER Pp 1142, with 88 illustrations London Henry Kimpton 1951 Price 105s

This large new textbook of clinical endocrinology is from the Mount Sinai Hospital, New York It follows the traditional style, is well written and carefully documented Illustrative case records add to its interest It is a pity that the appendix of laboratory tests does not contain an assessment of the value of these tests The authority of the book may encourage an unwarranted faith in some of the methods, such as those for urinary corticosteroids The photographs, especially those in colour, are not up the to standard of the text It would be better to omit the term " Simmonds' Cachexia " which emphasises an inconstant feature of the disease. But these are minor criticisms, and the author is to be congratulated on his courage and skill in producing a book which should be of real value to students of endocrinology.

Major Symptoms in Clinical Medicine By JOHN ALMEYDA, M R C P, M R C S, D P H Pp viii+335 Vol II London Henry Kimpton 1951 Price 25s net

Like the first volume of this book, volume two discusses the applied anatomy and physiology of each system before the main symptoms in each section are described This second volume contains sections on neurological, psychological, locomotor and endocrine symptoms The whole book is written in a clear, lucid and direct style and should prove very useful for undergraduates and postgraduates

The Thyroid By THOMAS HODGE MCGAWACK Pp 646, with 72 figures and 22 tables London Henry Kimpton 1951 Price 95s

The literature dealing with the thyroid grows rapidly This book aims to present a large scale, up to date review of the chemistry and physiology and to analyse thyroid disease in the light of our newer knowledge It succeeds in these aims and at the same time entertains the reader with an interesting historical section It is a little surprising to read that patients who receive antithyroid drugs for hyperthyroidism should have a determination of the basal metabolic rate and a complete blood count before each visit to the clinic However, there is little to criticise in the book, which is a comely and intelligent guide through the maze of papers on the thyroid

NEW EDITIONS

Handbook of Tuberculosis Schemes in Great Britain and the Commonwealth Thirteenth Edition Pp 370 London National Association for the Prevention of Tuberculosis 1951 Price 30s net

The coming into force of the National Health Service Act has necessitated the re-writing of this Book Tuberculous patients move about like other people, and the Tuberculosis Physician has for many years depended upon this book for information regarding the services available in other areas He will find all that he wants to know in this new and enlarged edition

American Illustrated Medical Dictionary By W A N DORLAND, A M, M D, F A C S Twenty second Edition Pp xxvi+1736, with many illustrations London W B Saunders 1951 Price 50s

This book which first appeared in 1900 has long been esteemed a classic It is run by an editorial board helped by the contributions of a large number of specialists The present edition includes thousands of new terms and scores of new illustrations which bring it up to date in the various fields of medicine and allied sciences A valuable feature of the work is the large number of useful tables

This standard work is probably the leading medical dictionary in the English language

Fractures, Dislocations and Sprains By J A KEY and H E CONWELL Fifth Edition Pp 1232, with 1195 illustrations London Henry Kimpton 1951, Price 115s net

The new edition of this well-known American text-book has just appeared and though many of the least valuable illustrations have been deleted, little reduction in the book has been achieved since much new material in the way of new methods or modifications of old has been added The authors rightly make little claim to originality, and the methods described are mostly those in general use None the less, the book is well written and interesting to read since these methods are fully described and lavishly illustrated

There is an admirable chapter on injuries of the spine in which all types of such injuries are fully described in an up-to-date fashion

In other parts of the book there is much upon which surgeons in this country might have different ideas Skeletal traction to the lower end of the femur is virtually given up here but there are many illustrations of it in the text-book It is interesting to read of general treatment to periarthritis of the shoulder in the shape of "a low caloric diet, low in fats and rich in green vegetables and fruit, and a teaspoonful of sodium phosphate in a glass of water on arising in the morning" The authors believe that shoulder function in a ruptured supra-spinatus is restored without operation It seems strange, too, to amputate in a case of congenital tibial lower third fracture

The production of this volume is far below the standard of Scottish publishers, but it is a useful book for those for whom it is written—students, practitioners and surgeons

BOOKS RECEIVED

COOPE, Dr ROBERT The Quiet Art (*E & S Livingstone Ltd, Edinburgh*) 12s 6d net

DAVIDSON, MAURICE, M A, D M, B CH (OXON), F R C P (LOND), and SMITHERS, DAVID W, M D (CANTAB), M R C P (LOND), D M R, and TUBBS, OSWALD S, M A, M B, B CHIR (CANTAB), F R C S (ENG) The Diagnosis and Treatment of Intrathoracic New Growths (*Oxford University Press, London*) 42s net

DYKE, S C, D M (OXON), F R C P (LOND), General Editor Recent Advances in Clinical Pathology Second Edition (*J & A Churchill Ltd London*) 40s net

ELLER, JOSEPH JORDAN, B S, M D, and ELLER, WILLIAM DOUGLAS, M D Tumors of the Skin Second Edition (*Henry Kimpton, London*) 105s net

HAULTAIN, W F T, O B E, M C, B A, M B, B CH, F R C P ED, F R C S ED, F R C O G, and KENNEDY, CLIFFORD, M B, CH B, F R C S ED, F R C O G A Practical Handbook of Midwifery and Gynæcology Fourth Edition (*E & S Livingstone Ltd, Edinburgh*) 24s net

KEYNES, GEOFFREY, M D, F R C S, F R C O G Ambroise Pare (*Falcon Educational Books, London*) 15s net

MONROE, ROBERT T, M D Diseases in Old Age (*Harvard University Press, Cambridge*) 32s 6d net

MORISON, J EDGAR, M D, B SC Fœtal and Neonatal Pathology (*Butterworth & Co (Publishers) Ltd, London*) 50s net

Originally Edited by MUSSER, JOHN H, B S, M D, F A C P Fifth Edition by WOHL, MICHAEL G, M D, F A C P Internal Medicine Fifth Edition (*Henry Kimpton, London*) 105s net

WALKER, JOSEPH V, M D, M R C P, D P H Health and the Citizen (*Holts & Carter, London*) 10s 6d net

WATSON JONES, Sir REGINALD, B SC, M CH ORTH, F R C S, F R A C S (HON), F A C S (HON) Fractures and Joint Injuries Volume I Fourth Edition (*E & S Livingston Ltd, Edinburgh*) £6 per set of 2 volumes

Revised by WILSON, ANDREW, M D, PH D, F R F P S, and SCHILD, H O, M D, PH D, D SC Clark's Applied Pharmacology Eighth Edition (*J & A Churchill Ltd, London*) 37s 6d net

Any Questions? First Series (*British Medical Association, London*) 7s 6d

Edinburgh Medical Journal

March 1952

ON OCCLUSION OF THE ABDOMINAL AORTA

By CATHERINE C BURT, B Sc, M B, Ch B, Sir JAMES LEARMONTH, K C V O, C B E, Ch M, F R C S E, and R L RICHARDS, M D, M R C P E

(*From the Department of Surgery, University of Edinburgh*)

PART III—AORTIC EMBOLISM

Clinical Observations

(*a*) MATERIAL

IN our series there were 16 patients who presented the clinical features of sudden occlusion of the aortic bifurcation (Table VII) In all the occlusion was due to embolism, although in 2 (Cases 7 and 8) the embolus itself did not occlude the bifurcation and the symptoms of aortic occlusion were probably produced by reflex vasospasm, in a third (Case 6) simultaneous embolism of both femoral arteries occurred The ages of the patients ranged from 4 years to 82 years, and there were 5 males and 11 females Eight (Cases 1, 7, 8, 9, 10, 12, 13 and 15) of the patients were suffering from rheumatic heart disease with auricular fibrillation, and the source of the embolus was presumed to be a thrombus in the left atrium, 3 patients (Cases 2, 4 and 6) were fibrillating but did not have rheumatic heart disease, in 1 patient (Case 3) the origin of the embolus was a mural thrombus in the left ventricle following a myocardial infarct, and in another (Case 5) the embolus originated in the calf veins and reached the arterial circulation through a patent foramen ovale In 3 cases the occlusion occurred during the post-operative period, after ligation of the saphenous vein (Case 11), after salpingectomy (Case 14) and after appendicectomy (Case 16) The exact course of events leading to the lodgement of the aortic emboli in the last 3 cases is uncertain In Cases 11 and 14 pulmonary embolism had occurred previous to the aortic occlusion and it is suggested that as a result of the pulmonary infarctions propagating thrombi formed in the pulmonary veins and were swept into the systemic circulation, alternatively the emboli may have been of the paradoxical type and have had their origin in the same veins as did the pulmonary emboli In Case 16 the embolus probably came from the left ventricle

In 9 of the 16 cases other embolic episodes occurred before and/or after the aortic occlusion (Table VII)

(*b*) THE CLINICAL PICTURE

The exact history and findings on examination depend upon the behaviour of the embolus It may block first one common iliac artery and then the other, so that one limb is affected before the other , or it may be impacted more firmly into one common iliac artery so that the opposite limb still receives a trickle of blood Occasionally a small embolus which is not large enough to obstruct the aortic bifurcation may produce a clinical picture which at first suggests aortic embolism ; within an hour or two, however, it becomes apparent that recovery in one or both lower limbs is taking place

TABLE VII

Aortic Embolism Details of Cases

Case	Sex	Age	Origin of Embolus	Other Emboli		Time Interval *	Treatment	Result
				Pre aortic	Post aortic			
1	F	58	Rheumatic carditis Auricular fibrillation	R femoral	Sup mesenteric L renal	7 days	Conservative Amp L leg	Died of mesenteric embolism 6 weeks later
2	F	76	Auricular fibrillation	—	—	5 days	Conservative Bilat amp	Died 3 months later, cardiac failure
3	M	57	Myocardial infarction	—	—	1¼ hours	Nil	Died within 24 hours Carcinoma recti
4	F	53	Auricular fibrillation	—	—	48 hours	Conservative	Died 3 weeks later
5	M	63	Paradoxical L calf veins	L cerebral R brachial	—	—	Nil	Died Autopsy diagnosis
6	F	82	Auricular fibrillation	—	—	6 weeks	Nil	Died 2 weeks later
7	M	56	Rheumatic carditis Auricular fibrillation	—	R cerebral	3 hours	Exploration of L popliteal artery	Died of cerebral embolism 6 months later
8	F	40	Rheumatic carditis Auricular fibrillation	—	—	3½ hours	Conservative	Recovered
9	F	50	Rheumatic carditis Auricular fibrillation	Multiple visceral	—	11 hours	Embolectomy Amp R leg	Died 36 days later Moist gangrene
10	F	41	Rheumatic carditis Auricular fibrillation	—	—	18¼ hours	R femoral embolectomy	Died immediately post operatively
11	F	57	Post operative	R pulmonary	? cerebral	2 hours	Embolectomy	Alive and well 4½ years later
12	F	55	Rheumatic carditis Auricular fibrillation	—	R cerebral (2)	4 hours	Embolectomy	Immediate recovery Died 5¼ months later of cerebral embolism
13	M	47	Rheumatic carditis Auricular fibrillation	—	—	5 hours	Embolectomy	Alive and well 18 months later
14	F	36	Post operative	L pulmonary x 3	—	9 hours	Embolectomy	Alive and well 5¼ years later
15	F	42	Rheumatic carditis Auricular fibrillation	R ext iliac R popliteal	—	24 hours	Embolectomy	Died 36 hours later
16	M	4	Post operative	R renal L femoral R and L popliteal	—	15 hours	Embolectomy	Died 14 hours later

* Before patient seen in conservatively treated cases before embolectomy in operated cases

These points may be illustrated by considering in some detail the development of the clinical picture in our 16 cases For descriptive purposes we have arbitrarily divided the course of events during the first three days after the lodgement of an aortic embolus into *the onset* and *three stages*, the first six hours, from six to forty-eight hours and from forty-eight to seventy-two hours

(1) *The Onset*—In 12 of the 16 cases accurate information is available about the initial symptoms At the moment of onset, 9 patients were resting, either in a chair or in bed , the other 3 were standing.

One patient described a gradual onset, and one (a child) did not complain, the others gave a history of a sudden incident

Pain was the initial symptom in 8 cases, it was felt first in the legs in 4 cases, in the abdomen in 2 cases, in the lumbar region in one case and simultaneously in the lumbar region and in the legs in one case Within a matter of minutes pain and loss of power in the legs became the most important features in all cases The pain in the legs was described as cramp-like or "like a heavy weight" and was usually referred to the calf, that in the abdomen was also described as cramp-like All 8 patients described the intensity of the pain as "severe" Three patients who did not experience pain as the initial symptom complained first of sudden loss of power in the lower limbs, 2 soon experienced pain in the legs but the other patient insisted that she had "no pain anywhere" Of the 3 patients who were standing at the time of onset, 2 would have fallen had they not been caught by a relative, the other collapsed and was unable to walk but crawled to a door and called for help

In the majority of the cases symptoms appeared simultaneously in both lower limbs One patient noted that the right foot was affected before the left, one hour before the major episode, another complained of cramp-like pain in the right calf, examination of the limb at that time did not reveal any vascular or neurological disturbance

(ii) *The First Six Hours*—Six of the patients were seen within six hours of their first symptoms, the clinical picture varied considerably The most rapid development was seen in Case 11, within one and a half hours there was complete paralysis of the lower limbs, cyanosis extending to the inguinal ligament and sensory loss as high as the twelfth thoracic dermatome As a contrast, in Case 12 at one and a half hours active flexion of the hip, knee and toes on both sides was possible, loss of sensation was confined to the foot and outer side of the leg and only the toes and distal portions of the feet were blanched, the legs were mottled in appearance and the thighs pink

At four hours another patient with complete obstruction (Case 13) had paralysis below the knee on the right but on the left could plantar-flex the foot and had a flicker of voluntary power in the dorsiflexors of the ankle and in the long extensors of the toes Sensory loss on the right extended to the level of the adductor tubercle, on the left to the neck of the fibula on the lateral side and to mid-leg on the medial side Position sense was absent in all the joints of the toes and in both ankles The feet were white and the toes had a shrivelled appearance, the legs were pale, the skin did not blanch on pressure and the superficial veins were not collapsed and filled slowly when emptied by pressure

Two important observations were made on the 4 patients who presented signs of complete occlusion, (*a*) during the first six hours the joints remained mobile but not lax and in none of the cases were muscle contractures noted, and (*b*) in two cases at one and a half and four hours the knee and ankle jerks were absent , in a third at one and a half hours the knee jerks were present but the ankle jerks absent , in the fourth the reflexes were not tested

During the first six hours 2 patients showed signs of spontaneous recovery and it became apparent that the original diagnosis of an embolus occluding the aortic bifurcation was incorrect

Case 7 —A man, aged 56, had suffered from rheumatic heart disease for many years and was fibrillating Three hours before admission he noted the gradual onset of pain in both calves and slight pain in the lumbar region The pain in the legs increased in intensity and, after about ten minutes, he became conscious of numbness, tingling and loss of power in both legs, more marked in the left After thirty minutes the pain in the right leg subsided and he noted that he could move it better than the left, but he was unable to walk

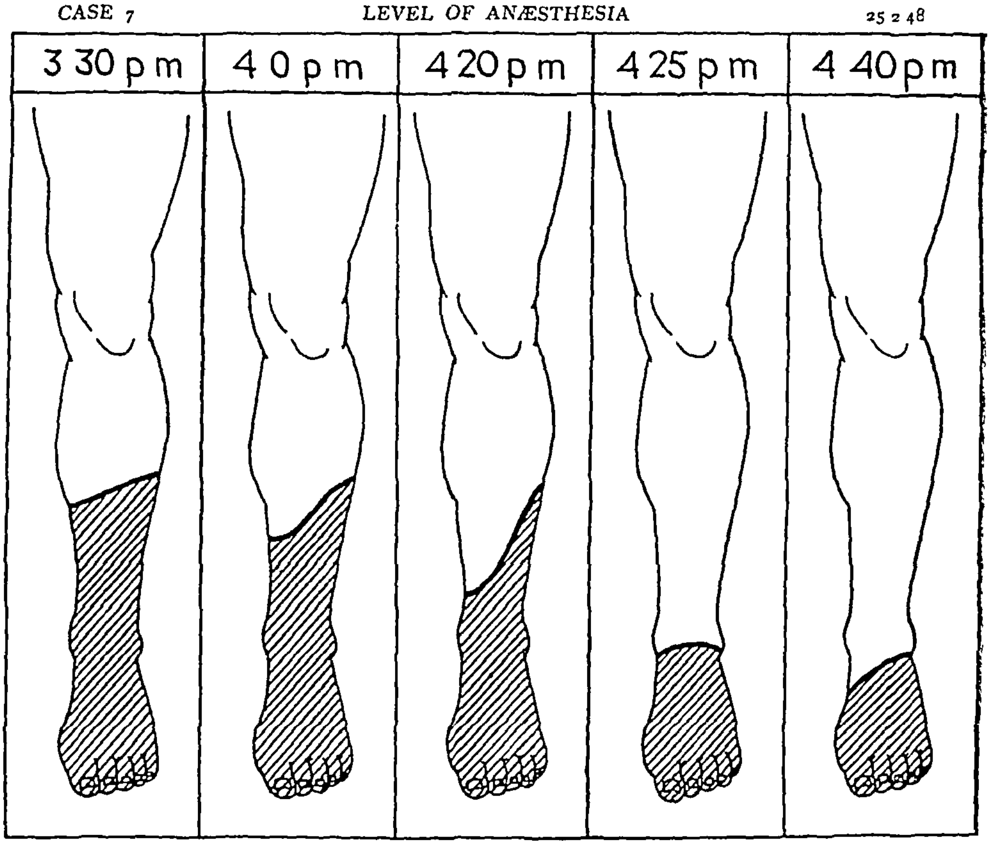

Fig 23 —Aortic embolism Case 7 —To show the rapid regression of anæsthesia in aortic pseudo embolism

On admission there was paralysis of the left leg distal to the knee and a level of analgesia 17 cm proximal to the medial malleolus There was no flexion contracture and the ankle jerk was present The foot was white, the leg cyanosed and the veins were empty The pulse could not be felt in the femoral artery On the right there was no motor paralysis , a strip of analgesia was present along the outer border of the foot and only the toes and distal

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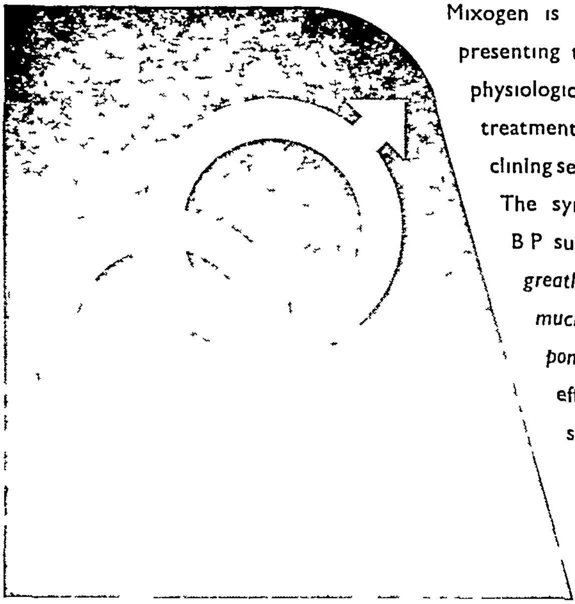

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third of the foot were blanched Pulsation was felt in the right femoral artery The right foot rapidly recovered The left leg at first showed a tendency to improvement, recovery was noted in both the calf and dorsiflexors of the foot and the sensory level receded distally (Fig 23) However, at six hours the calf muscle felt firm and was a little tender and the ankle jerk could not be elicited Because of these findings it was considered probable that a small embolus had lodged in the left popliteal artery and this vessel was explored It was found to be patent but not pulsating When it was opened, blood flowed from the incision—at first dark and sluggish, but soon a brisk non-pulsatile stream of bright red blood The artery was then opened distally and the origin of the anterior and posterior tibial arteries explored but an embolus was not found

The patient recovered from this episode but died six months later of cerebral embolism At autopsy the aortic bifurcation was not occluded, unfortunately the vessels of the lower limbs were not examined

TABLE VIII

Aortic Embolism State of Pulses in Cases Seen within Six Hours of Onset

Case	Time	Pulses								
		Aorta	External Iliac		Femoral		Popliteal		Posterior Tibial	
			Right	Left	Right	Left	Right	Left	Right	Left
3	1½ hr	Not felt	++	++	+ (thrust)	+ (thrust) *	—	—	—	—
	9 hr	Not felt	—	—	—	—	—	—	—	—
7	3 hr	N R	N R	N R	+	—	—	—	—	—
8	3½ hr	N R	N R	N R	+	±	—	—	—	—
11	2 hr	N R	N R	N R	—	feeble	—	—	—	—
12	4 hr	N R	N R	N R	—	—	—	—	—	—
13	5 hr	++ †	—	—	—	—	—	—	—	—

N R = Not recorded

* Left femoral artery palpable as thick non pulsatile cord
† Downward thrust Stops 5 cm above umbilicus

CASE 8—A 40-year-old housewife who was known to have had rheumatic carditis since the age of 18 was admitted three and a half hours after she had suddenly experienced severe pain in both calves and loss of power in the legs When first seen, the right lower limb was normal apart from coldness of the foot and absent pulses in the popliteal, dorsalis pedis and posterior tibial arteries On the left there was paralysis below the knee although a flicker of voluntary movement was seen in the calf, analgesia extended to knee level and the lower half of the leg and foot was white and cold A femoral pulse was felt on both sides, more easily on the right Progressive improvement occurred and at five hours both dorsiflexion and plantar flexion of the left foot and toe movements were present, analgesia was confined to the foot and the skin was pink at the ankle Without operation complete recovery followed

The state of the pulses in this group of cases is shown in Table VIII One and a half hours after the first symptoms in Case 3 pulsation was felt in the external iliac and femoral arteries, but in the latter the pulsation had a definite thrusting quality and it was considered that this represented a downward thrust transmitted from pulsation in the external iliac arteries This view was supported by the fact that the left femoral artery could be felt as a firm rounded cord in the femoral triangle Seven and a half hours later pulsation could no longer be felt in the external iliac arteries and it was then that the diagnosis of aortic occlusion was made This patient had had a myocardial infarct and at autopsy a large loosely adherent mural thrombus was found in the left ventricle , multiple emboli probably originated from this thrombus. The significance of the pulsation in the femoral arteries in Cases 7 and 8 has already been considered In Case 11 feeble pulsation was felt in the left femoral artery only, but in Cases 12 and 13 both femoral pulses were absent In Case 13 pulsation of the aorta in the epigastrium was forcible and a very distinct downward thrust was felt which ceased 5 cm. above the umbilicus

(iii) *From Six to Forty-eight Hours*—Seven patients (Cases 3, 7, 8, 10, 14, 15 and 16) were first seen during this period or were followed through from the earlier period without embolectomy We can exclude from further consideration those 2 patients (Cases 7 and 8) in whom at six hours it was already apparent that spontaneous improvement was occurring In the remaining 5 cases the outstanding finding which was not observed in any case during the first six hours was the presence of contractures of the muscles of the calf, of the anterior tibial group of muscles, or of both The contracture was noted in Case 3 at nine hours but was not recorded in Case 14 after the same time interval In Case 10 at eighteen and a half hours a well-marked flexion contracture of both ankles was noted, and in Case 15 at twenty-four hours a similar contracture was present and the calf muscles were described as " doughy and slightly tender " Associated with these contractures the toe and ankle joints became stiff and the tendons of the contracted muscles stood out as tight, prominent cords In general the extent of the motor and sensory paralysis was greater in this group than in the cases seen earlier All these patients showed complete motor paralysis below the knees and a sensory level at or proximal to mid-thigh Signs of gross impairment of the circulation to the lower limbs was present in all, but gangrene was not observed However, in Case 3 at twenty-two hours commencing gangrene of the penis was noted

The fifth case in which muscle contractures were noted presented certain unusual features —

Case 16 (Mr F H Robarts's case) —A boy, aged 4 years, was operated on for acute appendicitis , a gangrenous appendix was removed and a small abscess overlying the right iliac vessels was drained For the first forty-eight hours his progress was satisfactory but during the next twenty-four hours he vomited twice At this time he appeared dehydrated and there was abdominal distension but he did not complain of pain An intravenous saline infusion was given into the right long saphenous vein On the evening of the third post-operative day he became restless and restlessness continued through the night The next morning his left leg was noted to be mottled, swollen and cold On the afternoon of the fourth post-operative day, the findings were as follows —

The child was restless but did not complain of pain During the examination he volunteered the information that his feet were " sore " There was paralysis of both lower limbs below the knee, voluntary activity was present in the thigh muscles on both sides, but accurate assessment of this could not be made On the right a full range of passive movement was obtained at all joints, on the left flexion contractures were noted in the calf muscles and toe flexors and these muscles felt " doughy " but were not tender Both knee and ankle jerks were absent and stimulation of the soles did not elicit any response in the great toes The level of analgesia to pinprick was at the ankle on the right and at the knee on the left The left leg was slightly swollen but the foot and toes had a shrivelled appearance, the right foot and leg were normal in this respect The right foot was blanched and the veins were poorly filled, the left foot was pallid, the toes were cyanosed and the leg was mottled Both limbs were cold, the right to mid-leg, the left to mid-thigh Pulsation could not be felt in any vessel in either limb

The time of onset in this case cannot be determined, but comparison of the findings with the clinical picture in the other cases leads us to conclude that the left leg had been ischæmic, certainly for more than six hours and probably for twelve hours

During this period one patient (Case 10) showed evidence of some spontaneous recovery in the left leg, this was associated with return of the femoral pulse, regression of the sensory level and *almost complete disappearance* of the flexion contracture of the ankle

(iv) *From Forty-eight to Seventy-two Hours* —Only one patient (Case 4) was observed during this stage There were slight flexion contractures of the ankles but the toe joints were lax Complete paralysis of the lower limbs was present and the sensory levels were at the junction of the middle and lower thirds of the thighs Pulsation in the aorta was not felt, but the abdomen was distended There was no palpable pulse in any of the arteries in the lower limbs The feet and distal two-thirds of the legs were cyanosed and did not blanche on pressure Proximal to this was a zone of livid red discolouration which did blanche on pressure The feet and legs were slightly swollen

(v) *Summary* —These three stages into which we have arbitrarily divided the clinical picture during the first seventy-two hours after an acute arterial occlusion are shown in Table IX It must be stressed that the times at which one stage passes into the next are not fixed but vary from case to case and depend upon a number of factors such as the completeness of the block, the degree of reflex vasospasm and the rapidity with which a collateral circulation can develop What we wish to emphasise is that, in the evolution of the clinical picture after an acute arterial occlusion, whether at the aortic bifurcation or in a more peripheral vessel, it is possible to recognise three distinct stages an initial stage in which signs of paralysis develop but muscle contractures are not observed or are minimal , a second stage in which muscle contractures develop, joints become stiff and tendons of contracted muscles stand out as firm cords , and, if the ischæmia persists, a third stage in which contractures disappear, the muscles soften, the joints become loose and the limb swells If an accurate prognosis is to be given, it is important to recognise the stage that has been reached

(*c*) The Course of Events in Cases not Operated upon

Of the 16 cases, one-half did not have embolectomy performed Of these 8 cases, 2 (Cases 7 and 8) recovered but in both the obstruction was not complete One of these patients died later from a cerebral embolus (Case 7), the other is still alive but is severely crippled by her cardiac disease The remaining 6 patients (Cases 1-6) died, and in all cases the aortic embolus undoubtedly contributed to the fatal outcome In one of these patients the presence of an aortic embolus was not suspected before death , the remaining 5 patients died twenty-four hours, three weeks, six weeks, eight weeks and three months after the lodgement of the embolus The case in which the presence of an aortic embolus was not suspected before death (Case 5) is of interest because it is the only case in the series in which infarction of the bowel occurred The bifid embolus, which originated in the veins of the left calf and passed through a patent foramen ovale, lodged in the orifices of the cœliac axis and superior mesenteric arteries, and obstructed the inferior mesenteric artery (Fig 24) so that the intestines were suddenly completely deprived of blood The patient who died within twenty-four hours (Case 3) did not develop gangrene of the lower limbs but signs of impending gangrene of the penis were noted before death It is noteworthy that, shortly before he died, this patient passed urine which did not contain

TABLE IX

Acute Total or Almost Total Ischæmia of Limb

Duration (hours)	Clinical Features	Prognosis
To 6	Motor and/or sensory palsy ± Digits in flexion ± Slight elastic resistance to passive extension	Complete or almost complete recovery
6 48	Motor and sensory palsy + Muscles firm/hard Digits stiff in flexion, ankle/wrist stiff, tendons tight prominent cords	*Early* —Complete or incomplete motor and sensory recovery Contracture and joint stiffness ± *Late* —No recovery of power or of sensation — contracture (muscle fibrosis)—joint stiffness Skin preserved—or tips of digits lost
48 72+	Motor and sensory palsy persist All joints lax—tendons no longer prominent Hard muscles soften gradually Limb swollen	Muscles dead, recovery not possible Fibrosis not possible Some skin may be preserved

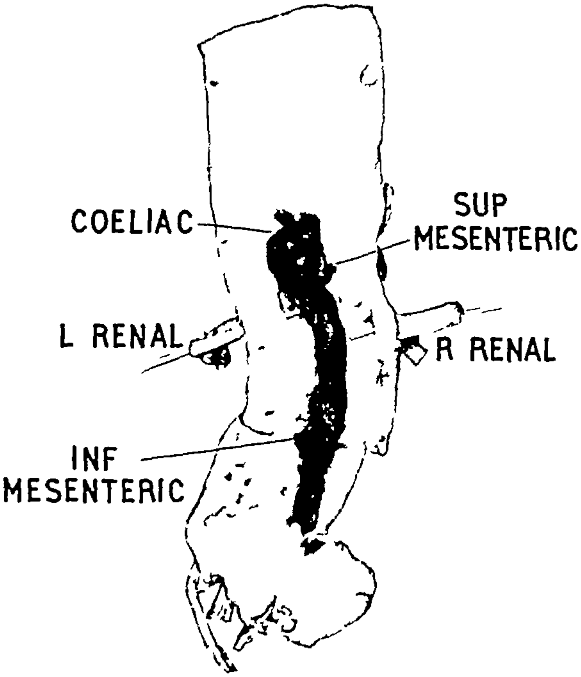

FIG 24 —Aortic embolism CASE 5 —To show occlusion of branches of aorta without complete occlusion of its lumen

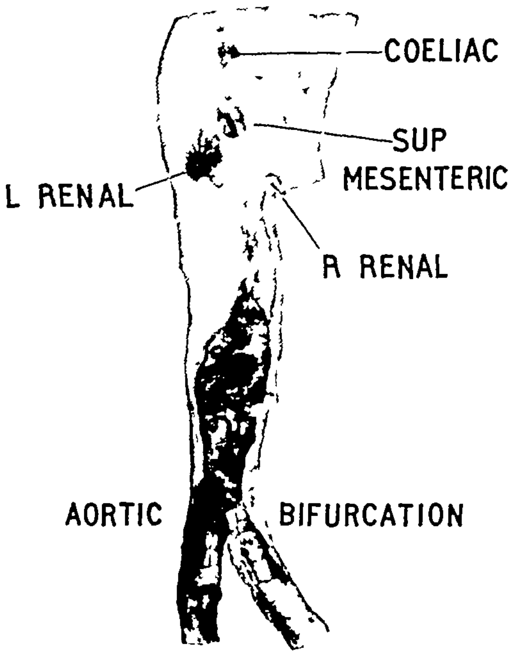

FIG 26 —Aortic embolism CASE 1 —To show extent of embolus and consecutive thrombus (Compare Fig 25)

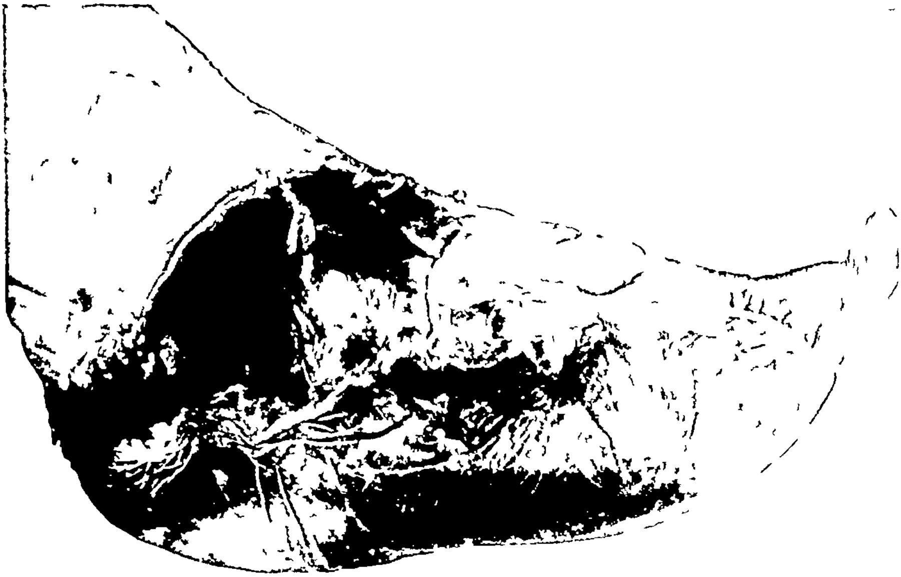

FIG 27 —Aortic embolism CASE 2 —To show extent of gangrene in foot

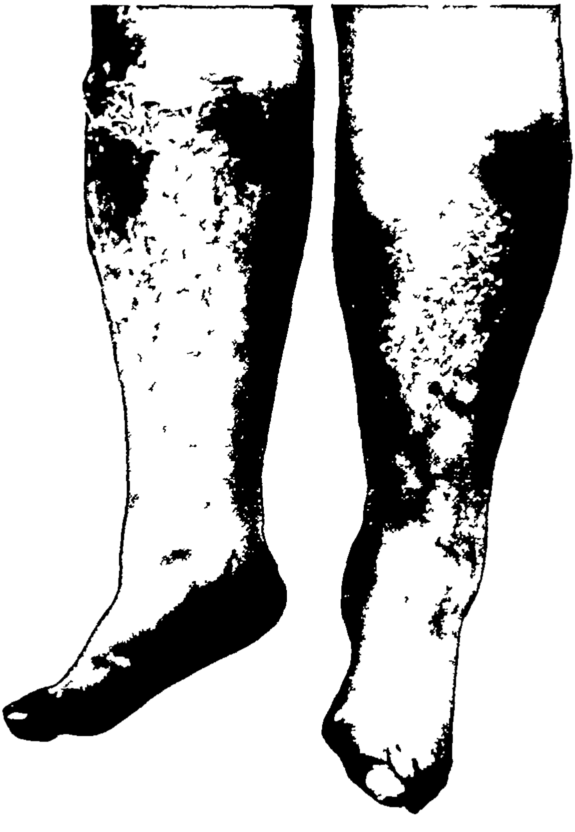

FIG 28 —Aortic embolism CASE 6 —To show extent of gangrene in legs

blood At autopsy the thrombus occluding the aorta was found to extend as high as the origin of the renal arteries but, since the upper portion of the thrombus was conical in shape, the openings of these vessels were not occluded The pelvic colon, rectum and anus had been removed previously for carcinoma of the rectum The remaining segments of the intestine, and the bladder, were not ischæmic

Two of the 3 patients who survived for some weeks required amputations, one of the left leg and the second of both legs, the third patient died of cardiac failure before amputation could be performed

CASE 1 12 7 49

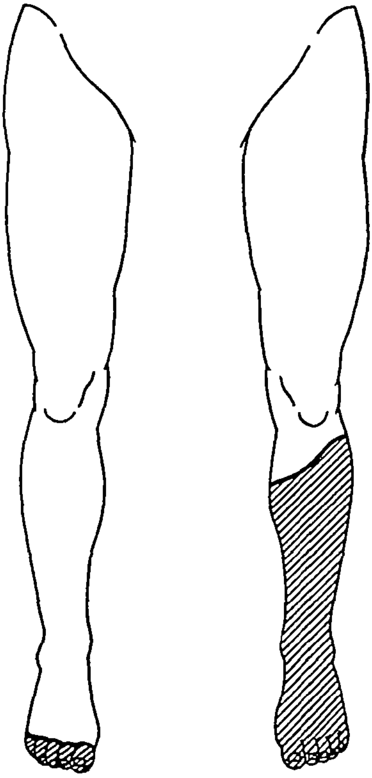

FIG 25 —Aortic embolism CASE 1 —To show sensory levels

CASE 1 —This patient was first seen seven days after the estimated time of lodgement of the embolus She gave a history indicating a previous embolic episode in the right lower limb seven months earlier The feet were held in plantar flexion and there was a slight flexion contracture of both ankles The toes were mobile On the left there was complete paralysis below the knee, and the calf was swollen, tense and acutely tender On the right there was voluntary power in the calf muscle, tibialis anterior and peronæi, but the long extensors of the toes and all the small muscles of the foot were paralysed The sensory level on the left was just below the knee (Fig 25), on the right only the toes were insensitive and pinprick on the sole produced a deep burning sensation Sense of position was present in the joints of the right toes but was ent in those of the left toes, and in the left ankle unless the foot was dorsi-ed sufficiently to stretch the painful calf muscles The left foot and leg ere blue, cold and swollen, the veins were empty and there had been extravasation of blood into the tissues On the right the toes were cyanosed but there was a small blistered area on the dorsum of the foot The aorta could be felt pulsating strongly at the level of the umbilicus, but distal to this the only pulse felt was a faint right femoral

The condition of the left leg did not improve and two weeks later a guillotine amputation at mid-thigh was performed The right leg improved at first, but after the amputation of the left leg its condition deteriorated slowly and amputation of the second limb would probably have been required if the patient had not died suddenly with symptoms suggesting a mesenteric embolus This diagnosis was confirmed at autopsy, recent emboli were found in the superior mesenteric and left renal arteries, and the cœliac axis and aortic bifurcation were both occluded by older emboli (Fig 26)

Case 2—This elderly lady was seen five days after the lodgement of an embolus At this time there was evidence of a complete aortic block, as judged by absence of both femoral pulses The degree of paralysis was greater on the left side than on the right, on the left the ankle and toes were quite lax, on the right flexion contracture of the calf muscles was present She was treated with anticoagulants Only the feet became gangrenous (Fig 27) and amputations had to be performed on the right at sixty days and on the left five days later Her condition gradually deteriorated after the second amputation and she died seventy-eight days after her embolism At autopsy "the aorta was plugged by old, brown, tough ante-mortem thrombus," which extended into both common iliac arteries The femoral arteries were occluded by thrombi which were considered to be of more recent origin than the thrombus in the aorta and iliac vessels

Case 6—One morning, on rising, a lady of 80 had a sudden feeling of giddiness followed by loss of power in both legs Six weeks after this episode there was dry gangrene of the feet and moist gangrene of the distal two-thirds of both legs (Fig 28) Faint pulsation could be felt in the proximal part of Scarpa's triangle Auricular fibrillation had been present for some weeks, it was thought probable that a "saddle embolus" had split at the aortic bifurcation and that portions of it had been swept into both popliteal or common femoral arteries The patient's general condition never permitted amputation and she died fourteen days later At autopsy the heart was found to be dilated and the coronary arteries were atheromatous The myocardium was healthy and none of the chambers contained ante-mortem thrombus The aorta was atheromatous and organised thrombus was adherent to a plaque a few centimetres above the bifurcation Both femoral arteries and the right profunda femoris artery were blocked by ante-mortem thrombus, the femoral veins were also thrombosed

(*d*) The Course of Events after Embolectomy

Eight patients were operated upon in an attempt to remove the occluding embolus In 4 cases the operation was unsuccessful —

CASE 9 (Mr F E Jardine's case) —Eleven hours after the initial symptom, operation was performed by Mr A R Murray The embolus was removed piece-meal through incisions made in both femoral arteries in the femoral triangles Although full circulation to the lower limbs appeared to be re-established at the end of the operation, the left lower limb did not recover and had to be amputated thirty-two days later The vessels at the amputation site were thrombosed A rapid, spreading moist gangrene of the stump developed and the patient died four days later At autopsy a large, partially organised clot straddling the bifurcation of the aorta was found On the right the thrombus extended to the bifurcation of the common iliac artery, but distal to that level the arteries were patent On the left recent clot occluded the iliac and femoral arteries to the level of the amputation

CASE 10 was operated upon eighteen and a half hours after the onset Although the initial symptoms and signs were those of an aortic embolus, there were *signs of recovery on the left side As the patient's general condition was* poor, a decision was made to explore the right femoral artery Portions of recent red clot were removed from this artery but a free flow of blood was not obtained It was thought that a block must be present more proximally but before any operative treatment for this was possible, the patient's condition rapidly deteriorated and she died as the incision in the thigh was being closed An autopsy was not obtained

CASE 15 —Operation at twenty-four hours the aortic bifurcation was exposed by a transperitoneal approach and the embolus removed through an incision in the right common iliac artery At the conclusion of the operation pulsation was felt in the left femoral artery but not in the right The patient did not speak after the operation, although she ate and drank, and thirty-six hours later she died During the post-operative period the contractures in the calf muscles and toe flexors became more severe (Table XI) and there was no evidence of sensory or motor recovery in either lower limb

At autopsy it was found that the whole of the aortic embolus had been removed Old emboli were found in the right external iliac artery and in the right femoral artery There was a recent thrombus in the left popliteal artery (Fig *29) and embolism of both anterior cerebral arteries*

CASE 16 —The interval between lodgement of the embolus and operation in this case cannot be estimated accurately but we consider that it was about fifteen hours A transperitoneal approach was used and portions of clot were removed through incisions made in both common iliac arteries (Fig 30) At the end of the operation a free flow of blood was not obtained, and pulsation was not felt in either external iliac or femoral artery After the operation the child lived for only fourteen hours During this period contractures developed in the calf muscles and toe flexors on the right, and the contractures on the left became more severe (Table XI) No motor or sensory recovery was noted in either limb

At autopsy the aorta was found to be blocked by clot for 3 cm proximal to the bifurcation (Fig 31) The upper 1 cm of this clot was white and firm, and not adherent to the wall, the distal 2 cm were softer, red and slightly adherent Proximally a thin thread of soft red clot extended to the level of the renal arteries Distally the right common iliac artery was filled with old non-adherent white thrombus and a strip of recent red clot was adherent to the anterior wall of the left common iliac artery The left femoral artery was blocked at the origin of the profunda by old, firm, non-adherent white clot and both popliteal arteries were occluded by softer red clot The cœliac, superior mesenteric and renal arteries were patent but the right kidney contained numerous infarcts The inferior mesenteric artery was blocked by clot as far as it was followed (2 cm) The femoral veins, the iliac veins and the inferior vena cava were patent, with normal endothelium The small residual abscess overlying the right common iliac vessels had not caused any macroscopic inflammatory change in the vessel walls The pulmonary artery and its primary branches were healthy and did not contain thrombus nor was there any evidence of pulmonary infarction The heart did not show any developmental anomaly The valves were healthy and the only possible source of an embolus was a small area of roughened endocardium on the septal wall of the left ventricle overlying several small sub-endocardial hæmorrhages Two small fragments of ante-mortem clot were lying free in the cavity of the left ventricle

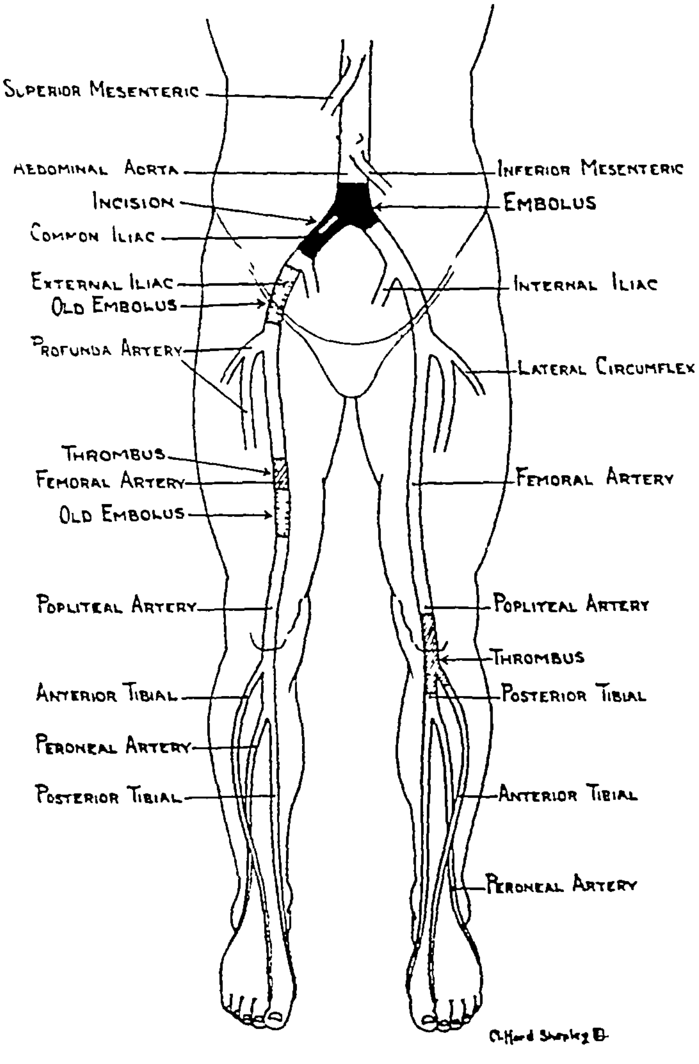

FIG 29 —Aortic embolism CASE 15 —To show extent of recent and old arterial blockage

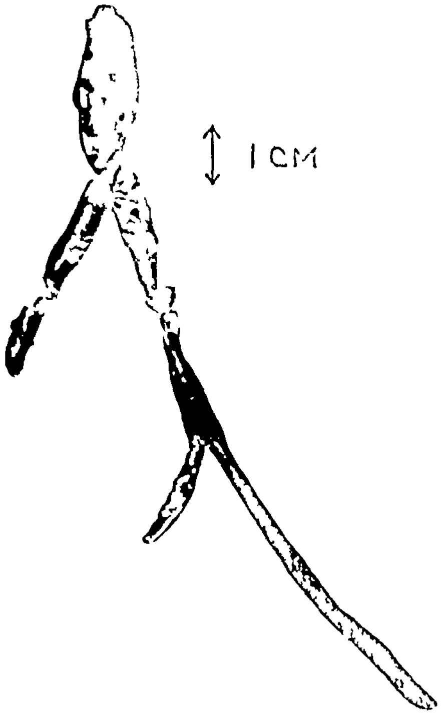

Fig 30 — Aortic embolism Case 16 — To show embolus and consecutive thrombus removed at aortic embolectomy

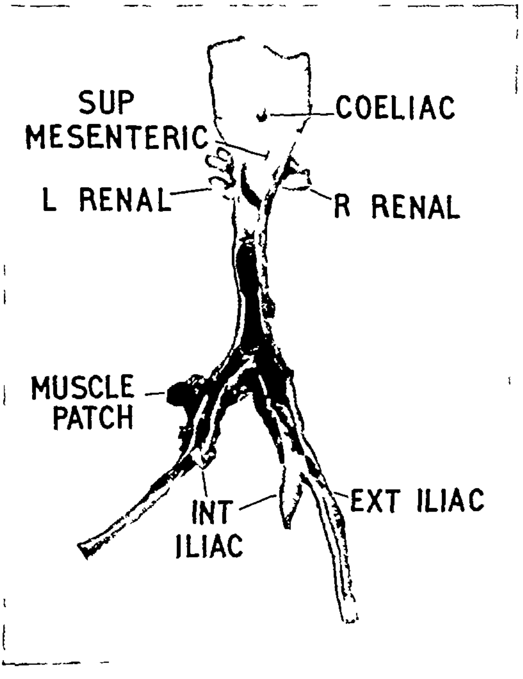

Fig 31 — Aortic embolism Case 16 — To show aorta at autopsy with further embolism and consecutive thrombosis (Compare Fig 30)

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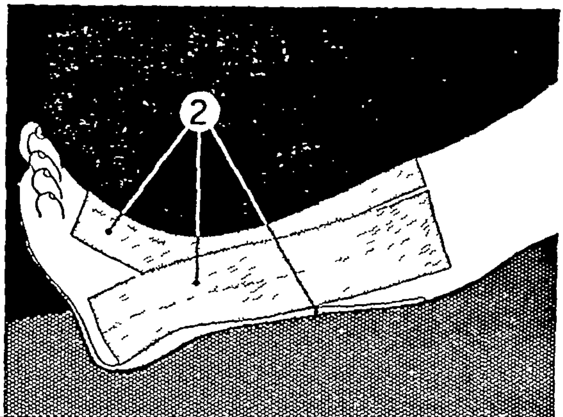
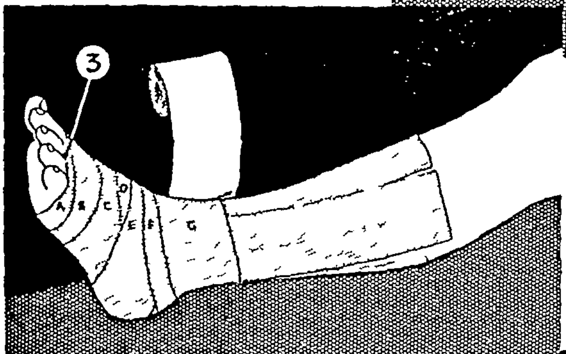
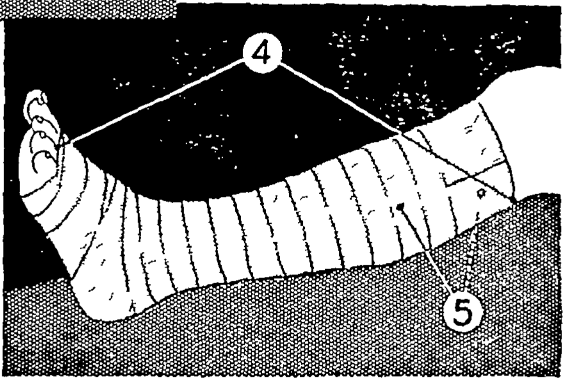




***3** Commencing at the webs of the toes, take two or three turns around the foot, dependent upon its length, and bandage around ankle enclosing heel as illustrated

4 Leg should be *covered* from webs of toes to a point just below the bend of the knee



5 Turns should overlap by at least half the width of the bandage (the yellow line down the centre of an Elastoplast bandage is a guide)

6 No creases

7 Firm and even pressure proportionate to the amount of induration and œdema present

* *Note bandaging may be made from toes upwards or knee downwards as desired*

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The course of events in the 4 successful cases (Cases 11-14) is shown in Fig 32 and Tables X-XIV These patients were operated upon

TABLE X

Aortic Embolectomy Time of Return of Peripheral Pulses after Operation

Case	Leg	Femoral	Popliteal	Posterior Tibial	Dorsalis Pedis	Perforating Peroneal
11	R	Immediately	3 weeks	11 months	1 month	—
	L	Immediately	3 weeks	11 months	1 month	—
12	R	? Immediately	? 5 hours	5 hours	5 hours	7 days
	L	? Immediately	—	1½ months	—	—
13	R	Immediately	? 1 week	18 days	3 months	—
	L	Immediately	1 week	? 24 hours *	1 week	3 months
14	R	Immediately	48 hours	19 days	12 months	—
	L	Immediately	—	Immediately	2 hours	—

* Absent at three months

TABLE XI

Aortic Embolectomy Contractures

Case	Time After Lodgement (hours)	Limb	Pre operative		Immediate Post operative		Post operative Recovery	
			Calf Muscle	Toe Flexors	Calf Muscle	Toe Flexors	Calf Muscle	Toe Flexors
11	2	R	—	—	±	—	24 hours	
		L	—	—	—	—	1 month	
12	4	R	—	—	—	—		
		L	—	—	±	—	10 hours	
13	5	R	—	—	—	—		
		L	—	—	—	—		
14	9	R	—	—	—	—		
		L	—	—	—	—		
15	24	R	+	+	++	++	No recovery	
		L	+	+	++	++	Patient died 36 hours after operation	
16	? 15	R	±	—	+	+	Patient died 14 hours after operation	
		L	+	+	+	+		

TABLE XII

Aortic Embolectomy Power of Muscles

Case	Time After Lodgement (hours)	Limb	Pre operative Paralysis	Post operative Recovery Time				
				Thigh	Calf	Tibialis Anterior	Toe Flexors Extensors and Peronæi	Small Muscles of Foot
11	2	R	Whole limb	9 hr	9 hr	9 hr	30 hr	2½ mth
		L	Whole limb	9 hr	30 hr	30 hr	1 week	2½ mth
12	4	R	Dorsiflexors of foot *			9 hr	9 hr	12 hr
		L	Below knee *		9 hr	9 hr	12 hr	2½ mth
13	5	R	Below knee *		36 hr	36 hr	Extensors 36 hr Flexors 14 days	14 days
		L	Small muscles foot †			18 hr	18 hr	36 hr
14	9	R	Whole limb	8 hr	8 hr	8 hr	8 hr	1 mth
		L	Whole limb	8 hr	8 hr	8 hr	8 hr	3 wk

* Paresis thigh

† Paresis thigh and dorsiflexors foot and toes

TABLE XIII

Reflexes after Aortic Embolectomy

Case	Reflex		Weeks after Embolectomy							Months after Embolectomy			
			0 2	2 4	4 6	6 8	8 12	12 16	16 26	6 12	12 18	18 24	24+
11	K J	R			+		+	+		+	±		+
		L			—		?	?		±	+		+
	A J	R			—		+	+		+	±		+
		L			—		—	±		++	+		+
	Plantar	R			↓		↓	↓		↓	↓		↓
		L			o		o	o		↓	↓		↓
12	K J	R	+	±	+		+	++					
		L	+	—	+		±	++					
	A J	R	—	—	—		+	++	Died at 5 months				
		L	—	—	—		—	±					
	Plantar	R	o	N R	N R		↓	?					
		L	o	N R	N R		↓	?					
13	K J	R	—	—	—		—			—			
		L	—	+	+		+			+			
	A J	R	—	—	—		±			±			
		L	±	±	+		+			+			
	Plantar	R	o	?	?		↓			↓			
		L	↓	↓	↓		↓			↓			
14	K J	R		N R					++		+		+
		L		N R					+		+		+
	A J	R		—					—		±		+
		L		+					+		+		+
	Plantar	R		N R					↓		↓		↓
		L		N R					↓		↓		↓

A blank column indicates that no observations were made during that period
N R = No record ? = Doubtful response
Knee and Ankle Jerks —+ = Normal reflex , ++ = Very brisk reflex , ± = diminished reflex , — = Absent reflex
Plantar — ↓ = Flexor response , o = No response

TABLE XIV

Aortic Embolectomy Vasomotor Studies

Case	Room Temperature ° C	Limb	Toe Temperature in ° C		Foot Blood Flow in ml /100 c c /min		Oscillometry Ankle Maximum	Time After Operation
			Average Resting	Maximum	Average Resting	Maximum		
11	18 0	L	24 3	N R	6 7	13 0	2 2	3½ yr
		R	24 0	N R	4 7	11 4	2 2	
12	15 5 18 0	L	15 5	N R	1 6	3 7 *		1 3 mth
		R	15 5	N R	1 7	4 8 *		
13	20 0	L	21 0	29 9 †	1 0	N R	1 5	3 mth
		R	23 0	30 25 †	1 3	N R	2 0	
14	22 0	L	25 8	32 2 ‡	13 5	17 0 ‡	3 5	4½ yr
		R	25 3	31 9 ‡	18 9	27 0 ‡	3 0	
Control (5) §	16 0 20 5	Average	23 2	33 3	3 6	20 9	3 1	
		Range	20 1-30 0	30 5 35 0	1 5 7 0	13 0 30 8	1 8 4 0	

* Reactive hyperæmia water in plethysmograph at 40° C
† Feet covered with a blanket
‡ Spontaneous vasodilatation while feet were exposed
§ Normal subjects with normal peripheral pulses

within ten hours of their initial symptom In 3 cases the aortic bifurcation was exposed by a transperitoneal approach and the clot removed through either one or both common iliac arteries In the fourth (Case 14) a bilateral transfemoral approach was used but the embolus was not successfully removed until the aorta had been exposed and the clot "milked" down into the femoral arteries

AORTIC EMBOLECTOMY—SENSATION

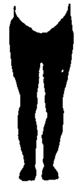
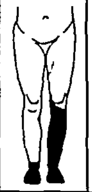
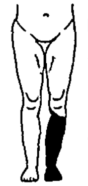
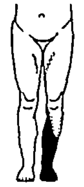
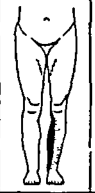
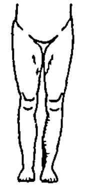
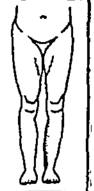
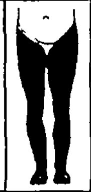
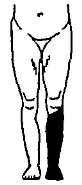
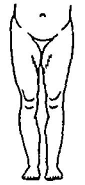
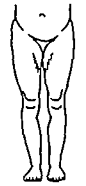
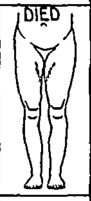
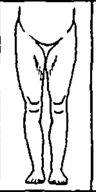
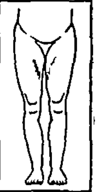
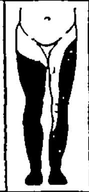
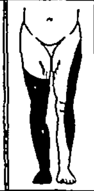
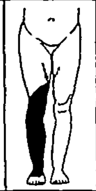
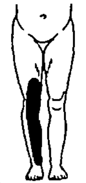
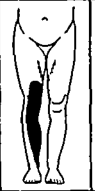
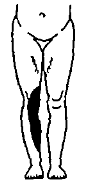
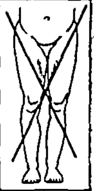
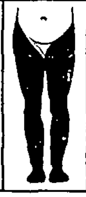
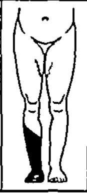
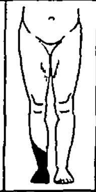
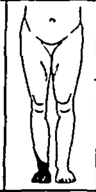
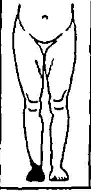
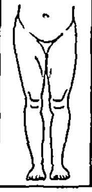
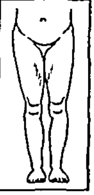
CASE NO	TIME IN HR AFTER LODGEMENT	PRE-OPERATIVE LEVEL	POST-OPERATIVE RECOVERY					
			0-24 HOURS	1-7 DAYS	UNDER 1 MONTH	UNDER 6 MONTHS	UNDER 12 MONTHS	12-18 MONTHS
11	2							
12	4							
13	5							
14	9							

FIG 32 —Aortic embolism CASES 11 14 —Recovery of sensation after aortic embolectomy

The return of the circulation to the lower limbs may be considered first At the conclusion of the operation in all 4 cases pulsation was present in both femoral arteries Despite this, the circulation to the limbs returned very gradually and in the majority of the cases forty-eight hours elapsed before the colour and temperature of the feet could be regarded as satisfactory This gradual return of the circulation is reflected in the delay that was observed in the return of the peripheral pulses (Table X) It will be noted that with the exception of Cases 12 and 14 in which the right and left posterior tibial and dorsalis pedis pulses respectively returned within a few hours, a delay of at least seven days occurred before the peripheral pulses returned

In these 4 cases further studies of the circulation in the lower limbs were made by instrumental methods Skin temperature of the toes and blood flow in the feet were measured with copper-constantan thermocouples and venous occlusion plethysmographs respectively, before and after inhibition of vasoconstrictor tone, in 3 of these patients pulsation at the ankle was measured with an oscillometer (Table XIV)

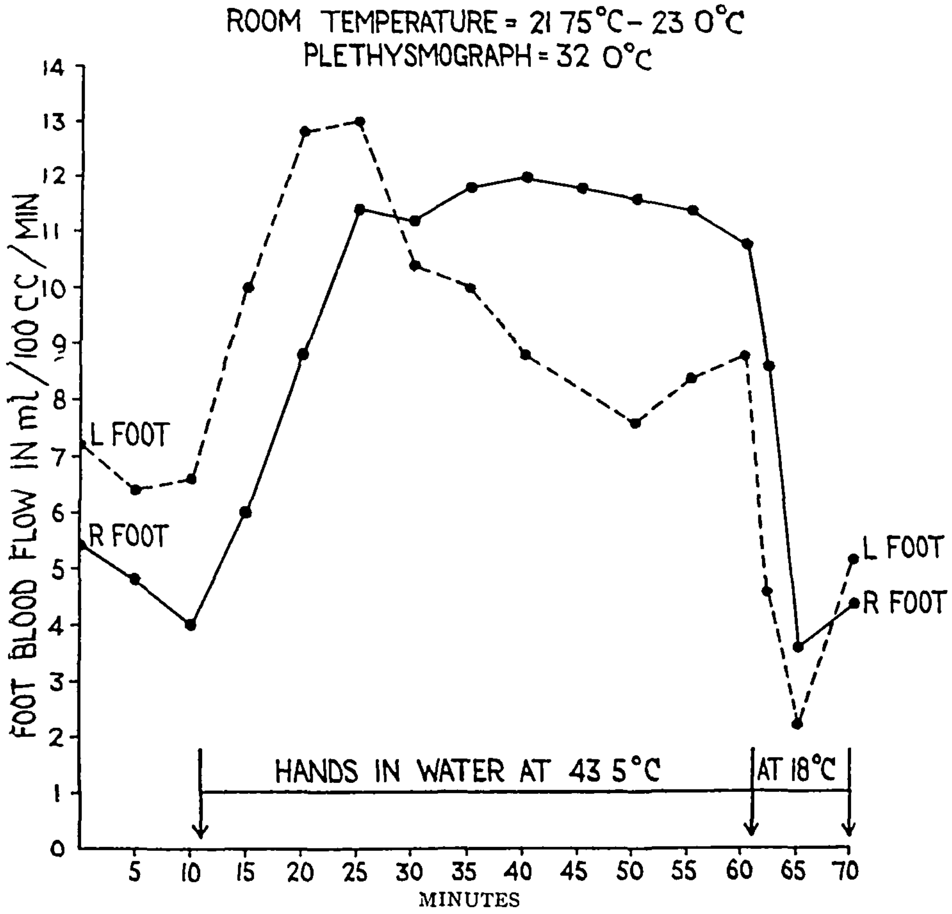


FIG 33 —Aortic embolism CASE 11 —Reflex vasodilatation test eleven months after aortic embolectomy

Little importance can be attached to the resting temperature of the toes and blood flow in the feet (Table XIV) as these vary greatly according to (1) the inherent vasoconstrictor tone of the individual, and (2) the environmental temperature, but it can be said that they did not differ significantly from normal

The maximum values of skin temperature or blood flow obtained when vasoconstrictor tone is inhibited give a measure of the vascular reserve in a limb (Table XIV) In Case 14 the temperature of the toes, blood flow in the feet and oscillometric readings indicated a normal circulation in both lower limbs with a reserve as great as that in the control subjects, this patient is able to walk several miles without pain In Case 12 the maximum blood flow in the feet obtained by a combination of indirect heating and direct heating was lower than normal The patient, however, was 55 years old and had suffered from auricular fibrillation for some years , it is not known whether vasomotor function in the lower limbs was normal before lodgement of the aortic embolus In Cases 11 (Fig 33) and 13 the maximum temperature of the toes and maximum blood flow in the feet were slightly below normal level in one limb and normal in the other , oscillometric readings were normal in Case 11 and only slightly below the normal range in one limb in Case 13

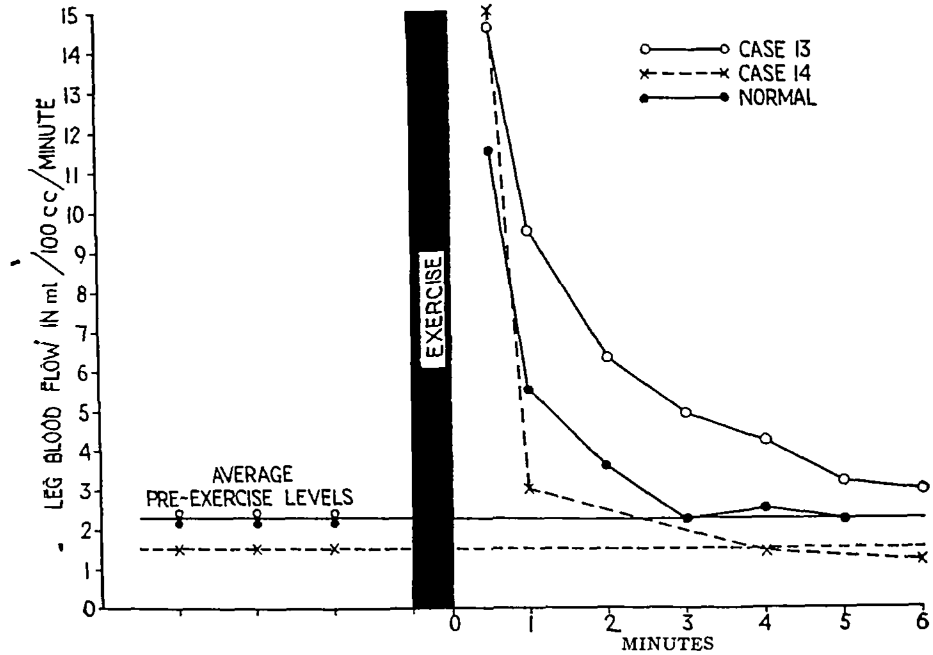


FIG 34 —Aortic embolism CASES 13 and 14 —Leg blood flow before and after exercise three months and twenty seven months respectively after aortic embolectomy

In 3 cases blood flow in the legs was recorded by a light celluloid plethysmograph before and after a period of exercise In comparison with similar readings in control subjects, one of the patients tested (Case 14) had a normal response (Fig 34) In the other 2 cases (Case 11, Fig 35, and Case 13, Fig 34), return of the blood flow to the pre-exercise level was delayed, a finding similar to that observed in cases of obliterative arterial disease with intermittent claudication (Shepherd, 1950 , Burt, unpublished observations) In neither case did the patient complain of pain during the test, but one of the patients (Case 11) states that, after walking for one mile uphill, she has to slow down because of pain in the calves , the other can walk two to three miles without difficulty

The course of recovery from the neurological disturbances has also been studied in some detail In a previous section we drew attention to the significance of the development of muscle contractures in those cases in which ischæmia had been present for more than six hours In none of the successful cases was a contracture noted before operation In Case 11 flexion contracture of both ankles, more marked on the left, was first noted after the operation , that on the right disappeared within twenty-four hours but on the left the contracture persisted for a month In Case 12 slight contracture of the left ankle was present for ten hours after the operation

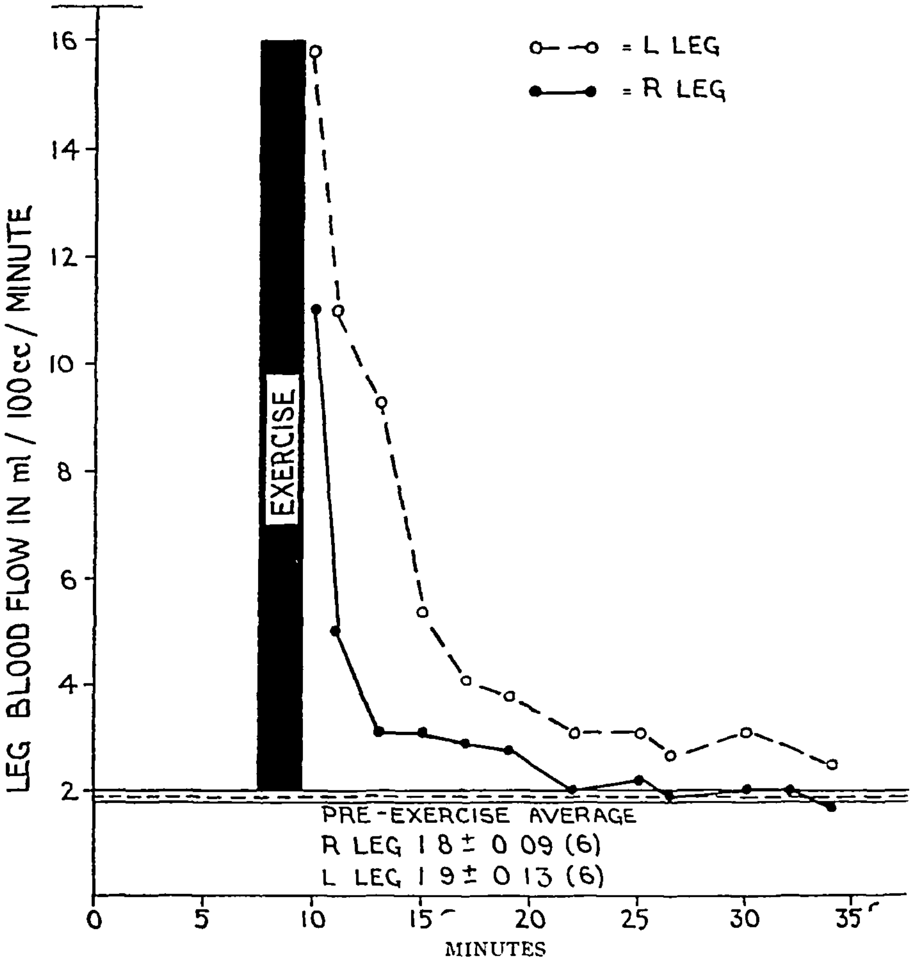


FIG 35 —Aortic embolism CASE 11 —Leg blood flow before and after exercise seventeen months after aortic embolectomy

The recovery of motor power in the limbs is shown in Table XII It will be noted that the thigh muscles recovered within nine hours, but that recovery in the calf muscle and tibialis anterior was delayed up to thirty hours in 2 cases, and that in 2 cases the long muscles to the toes did not recover for seven to fourteen days Assessment of function in the small muscles of the foot is often difficult, but our observations suggest that recovery in these muscles is often delayed for several weeks

Tendon reflexes are later in returning than is voluntary power

(Table XIII) The earliest return of a knee jerk which was absent before operation was after eighteen days (Case 13, left), but this patient's ankle jerk on the same side returned after three days Delays of up to eight months before recovery of the knee jerk and twelve months in the case of the ankle jerk, were recorded The plantar response was also lost in most cases and was noted to return after an interval which varied from seven days to eleven months

The recovery of sensation is illustrated in Fig 32 Three of the patients had an area of sensory loss which persisted for more than twenty-four hours Case 14 had a "stocking" area of anæsthesia on the right side which gradually receded and had disappeared in twelve months The other 2 patients (Cases 11 and 13) had a different distribution of sensory loss and the residual neurological disturbance in these 2 cases approximately three months after operation requires consideration in some detail

CASE 11 —Embolectomy performed on 10 7 47 Examination of lower limbs on 28 9 47 "The left foot is held slightly inverted, the right foot appears normal A full range of movement is possible at all joints The left leg is wasted compared with the right, measurement reveals 1 5 cm difference between the two calves Power for all movements is good on the right, on the left there is a general slight weakness of all muscles below the knee with a specific weakness of the peronæi, long flexors of the toes and extensor digitorum brevis The right knee jerk and ankle jerk are brisk, on the left the knee jerk is doubtfully present and the ankle jerk absent On the right all modalities of sensation are normal On the left there is an area of anæsthesia and analgesia on the inner side of the leg (see Fig 32) Over the outer side of the leg and dorsum of foot, touch and pain are appreciated but localisation is faulty On the sole the response to pinprick is delayed and unpleasant Position sense in the toes is poor, but vibration sense is normal The colour, temperature and nutrition of the feet are normal The left dorsalis pedis is the only pulse felt in either foot"

CASE 13 —Embolectomy on 16 5 50 Examination on 10 8 50 "The attitude of the feet is normal A full range of movement is possible at all joints The right thigh appears wasted compared with the left and measurement reveals 1 cm difference between the two Fasciculation is present in the right quadriceps and calf Power is good in all muscles of both lower limbs, but both quadriceps are slightly weak The right knee jerk is absent and the left knee jerk and both ankle jerks are present Both plantar responses are flexor On the right side there is a large area of hypæsthesia and hypalgesia over the medial aspect of the thigh and leg (Fig 32) The right sole is slightly hyperæsthetic Elsewhere response to pain and touch is normal Position sense is normal in the toes, but vibration sense is absent over the right foot, medial malleolus and tibial tuberosity There is no apparent vascular disturbance in either foot, on the right a good pulse is present in the posterior tibial and dorsalis pedis arteries, on the left only that in the dorsalis pedis is palpable"

The significance of these neurological disturbances will be considered later

The late results in these four successful cases were as follows —

CASE 11 —*This patient is alive and well four and a half years after* embolectomy She has a minimal residual weakness of the left foot

CASE 12 —This patient made an excellent recovery from aortic embolectomy but died five and a half months later from a cerebral embolus At autopsy the bifurcation of the aorta was found to be free from thrombus (Fig 36), and the suture line in the right common iliac artery was covered with endothelium

CASE 13 —This patient made a successful recovery from the embolectomy and ten weeks later Mr Andrew Logan removed his left auricular appendix to minimise the possibility of further embolic episodes During this operation a clot was expressed from the atrium The histological appearance of this indicated that it was a few days old The patient is alive and well eighteen months after embolectomy

CASE 14 —This patient is alive and well five and a half years after embolectomy Two years after the incident she was successfully delivered of a healthy child by Cæsarean section

DISCUSSION

Although numerically small, this group of cases of sudden occlusion of the abdominal aorta is comparable with most of the larger collected series

There is lack of unanimity regarding the sex incidence of aortic embolism Of Welch's (1910) 59 cases, 30 were females , on the other hand, Hesse (1921) found that aortic embolism was commoner in men, while both Rothstein (1935) and Greenfield (1943) state that the incidence is equal in males and females The preponderance of female patients in the present series is probably fortuitous although there is some evidence that in general embolic episodes occur more often in women than in men (Bull, 1922)

Aortic embolism is rare in infancy and childhood Rothstein (1935) collected 11 cases from the literature and added a twelfth , of these, 7 were in infants in the first year of life, and 3 in children aged 12 years The ages of the other 2 children were 3 and 3½ years , these were recorded by Allibert in 1828 (see Introduction) Few clinical details about these cases are available , even the sex of the children is not mentioned In neither case was the source of an embolus found and in both cases the aorta was the only artery occluded As Allibert's report antedated by some twenty years Virchow's exposition of the doctrine of embolism, these 2 cases may have been instances of thrombosis rather than embolism , indeed they are so regarded by Welch (1910) In our case (Case 16), the occlusion was considered to be due to an embolus , although the source of the embolus is uncertain, the other embolus in the left femoral artery, the infarcts in the right kidney and the fragments of ante-mortem clot in the left ventricle were sufficient evidence on which to make the diagnosis

The high proportion of cases in which the embolus originated in the heart (12 out of 16) and the frequency with which rheumatic carditis with auricular fibrillation was the pre-existing disease, are both observations which have been made by all who have examined the subject of aortic embolism The finding that other embolic episodes occurred in more than half of the cases is to be expected , if a patient with heart disease survives after an aortic embolism, it is the rule rather than the exception for him to die within a relatively short time, from the effects of a further embolic episode Since the source of the majority of emboli in cases of auricular fibrillation is the left auricular appendix, there is much to be said for the removal of the auricle in such a case, as was done in Case 13 So far as we are aware, he is the first recorded patient who has survived both aortic embolectomy and auriculectomy , a patient reported by Madden (1949) survived the embolectomy but died nine days after auriculectomy Although removal of the auricle may prevent further embolic episodes, there is some doubt whether in cases of mitral stenosis an embolus which occludes the aortic bifurcation ever originates in the *left auricle Welch (1910) pointed out that it is often difficult to believe* that an embolus large enough to occlude the bifurcation could have passed through the extremely stenosed mitral valve which is found at autopsy This problem is illustrated by Case 12 , the embolus removed at operation is shown in Fig 37, and when the patient died five months later the pathologist found the mitral valve " greatly thickened and narrowed so as to admit only the tip of the little finger " Mural thrombi in the ventricles are found at autopsy in approximately 13 per cent of cases of rheumatic heart disease (Garvin, 1941) and it seems reasonable to assume that the left ventricle may be a source of emboli which occlude the aortic bifurcation

The 2 cases in which the symptoms of aortic embolism were temporarily produced by emboli which apparently lodged in relatively small vessels of the lower limbs are of great interest Similar cases have been reported by Atlas (1942) and by Reynolds and Jirka (1944) There are two possible mechanisms which might produce this effect First, an embolism might temporarily occlude the aortic bifurcation and then slip down into one or other iliac artery and thence into an artery in the pelvis or lower limb Murray (1943) states, " In a fair proportion of these cases the immediate signs and symptoms suggest complete obstruction but under observation for a few hours the findings change, indicating that what was originally an impaction at the bifurcation of the aorta has changed, by the mass or masses, breaking and slipping down one or both sides to a lower level " An embolus which is large enough to do this could not be driven into such small vessels as the anterior and posterior tibial arteries It is, however, conceivable that in some of these cases the major portion of the embolus slips into an internal iliac artery where its presence cannot be detected, and only a fragment passes into the vessels of a lower limb The alternative explanation is that the embolus never lodges at the aortic bifurcation but when it impacts in a peripheral artery an intense degree of vasospasm is provoked which extends as high as the iliac vessels This is the view favoured by Atlas (1942) If we accept this hypothesis, however, *we must explain why bilateral symptoms are not produced in* every case of embolism of the vessels of a lower limb Perhaps the effect is produced only when an embolus fragments in such a way that embolic episodes occur simultaneously in both lower limbs (*e g* Case 6). Another tentative explanation for this interesting phenomenon is that it may be produced by a small embolus which lodges in a small artery near the bifurcation of the aorta, such as the median sacral artery, with the result that both common iliac and both external iliac arteries are thrown into intense reflex spasm (Learmonth, 1948)

The sudden onset, with pain as the main symptom in the majority of cases, is typical The cause of the pain in cases of arterial embolism is a subject which has been much discussed Most authors have assumed that the sudden onset of pain indicates the moment of lodgement of the embolus and have attributed the pain to the impact of the embolus upon the arterial wall (Danzis, 1933) or to arterial spasm (McKechnie and Allen, 1936) As the late Sir Thomas Lewis (1936*a*) pointed out, it is difficult to believe that the lodgement of a clot which is soft and has approximately the same specific gravity as blood can have any pronounced physical effect upon the vessel wall On the other hand, when embolectomy is performed it is often found that at the site of impaction of the embolus the artery is visibly distended and its wall slightly œdematous This was observed in 2 of our 4 cases (Cases 12 *and 15*) *Distension and œdema are probably not produced by the* lodgement of the embolus but are due to the continuous hammering effect of cardiac systole upon the impacted embolus Although this might appear to provide a satisfactory explanation for the pain of embolism, it must be admitted that experimental observations indicate that distension of an artery does not cause pain (Moore and Moore, 1933) In many cases the lodgement of an embolus is associated with a marked degree of reflex vasospasm , the 2 cases discussed above are examples of this phenomenon There is, however, no good evidence that arterial spasm is of itself a painful condition

Lewis (1936*a*) has pointed out that in cases of embolism pain occurs only when the part of the body which is made ischæmic contains muscular tissue , infarction of the brain, spleen and lungs * is usually painless whereas infarction of the heart, intestines or limbs is almost invariably associated with pain He held that the pain of embolism is not felt at the site of lodgement of the embolus but always distal to that point, and that it is usually referred to a muscular portion of the limbs Not all authorities are in agreement with Lewis on this point. For example, in a recent review Haimovici (1950) states, " The initial site of pain seems to be the region of lodgment of the embolus Its maximal severity at the onset is usually located at the level of the occlusion and much less often in the distal part of the affected limb "

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* Unless the infarct involves the pleural surface

In Lewis's opinion the pain is due to muscle ischæmia and does not occur at the moment of embolism but only after some minutes have elapsed If the affected limb is actively moved, the onset of pain is accelerated and its severity increased In support of this view, he quotes several cases in which embolectomy was performed under local anæsthesia , removal of the embolus did not relieve the pain, but as soon as the circulation to the limb was restored, the pain disappeared Danzis's (1933) experience has been the opposite , he states that pain is relieved as soon as the embolus is removed even although the restoration of the circulation is incomplete Our experience with cases of aortic embolism tends to support Lewis's hypothesis , the pain was most often referred to the calves and was described as cramp-like Pain in the abdomen and back can be attributed to ischæmia of the intestines or lumbar muscles as the result of obstruction, either by clot or by spasm, of the mesenteric or lumbar arteries Whatever the cause of the pain it is difficult to explain why some cases of embolism of the aorta (*e g* Case 12 *) or of a peripheral vessel are painless If the hypothesis that pain is due to muscle ischæmia and is aggravated by movement be accepted, then pain may be minimised or prevented by relative immobility of the ischæmic limb or limbs This may account for the absence of pain in Cases 12 and 16 In the former, at the time of the embolism, the patient was more seriously ill than any of the other patients and therefore probably did not move her limbs actively These observations are supported by de Takats (1942) who states that the pain of embolism may be absent in bed-ridden patients

The most important sign of occlusion of the aortic bifurcation is absence of pulsation in the arteries of both lower limbs, and especially in the femoral arteries Normally the pulse can easily be felt in the femoral artery just distal to the inguinal ligament and in the external iliac artery just proximal to the ligament When there is a history of sudden onset of pain and paralysis in both lower limbs, the pulses should always be examined and in these circumstances the absence of femoral pulses should at once suggest the diagnosis of embolism or pseudo-embolism of the aortic bifurcation It is well recognised that in cases of embolism it is often possible to feel " pulsation " in the artery distal to the site of impaction of the embolus This apparent pulsation is due to the forward thrust which is exerted upon the occluded artery at each pulse beat (Nordentoft's sign) This thrust is well marked in the aorta (*e g* Case 13), but we doubt whether it could be transmitted to the femoral arteries and there be mistaken for a pulse However, if the common femoral artery is occluded, it is possible to recognise the thrusting nature of the " pulsation " and sometimes to feel the femoral artery as a firm cord in the femoral triangle (Case 3)

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* In Case 16 the onset *may* have been painless Although the child did not complain of pain, he was very restless and when questioned directly admitted that his feet were " sore " It is well known that children often do not complain of pain in conditions which give rise to severe pain in adults

The motor and sensory paralysis which is a constant feature in all cases must be attributed to ischæmia, since no other factor is operative. The clinical evidence indicates that paralysis begins at the periphery and spreads centripetally From the observations on the present cases, it is apparent that there is great variability in the rapidity with which the paralysis develops and in its ultimate extent compare Case 11, in which within one and a half hours of the onset paralysis extended up to and including the twelfth thoracic segment, with Case 4 in which after forty-eight hours some movement of the thighs was possible and *the sensory level was at the junction of the lower and middle thirds of* the thighs Paralysis is observed not only when the abdominal aorta is occluded but also in cases of embolism of the main artery of a limb In the latter instance, paralysis is due to ischæmia of the peripheral nerves (Lewis, 1936*b*) When the aorta is occluded there is the possibility that ischæmia of the spinal cord or cauda might be an important factor in the causation of the paralysis The spinal cord is more sensitive to ischæmia than are peripheral nerves, one hour of total ischæmia is sufficient to produce permanent damage (Herter, 1889) Since the spinal cord normally ends at the level of the upper border of the second lumbar vertebra and the aortic bifurcation is usually at the level of the fourth lumbar vertebra, only a very large thrombus would occlude the upper pairs of lumbar arteries * and so interfere with the blood supply to the conus medullaris, but it is possible that the lodgement of an embolus at the aortic bifurcation might cause spasm of these arteries Even if either of these events were to take place, they could affect the blood supply only to the terminal portion of the spinal cord, and to produce sensory loss as high as the twelfth thoracic segment it is necessary to postulate a vascular disturbance in the cord at the level of the ninth thoracic vertebra If the spinal cord were damaged, disturbances of micturition should occur, but in none of our cases and in only a minority of those in the literature have these been recorded. Moreover, a successful embolectomy performed as late as nine hours after the initial symptoms has been followed by rapid and almost complete recovery from the paralysis, and therefore it seems improbable that ischæmia of the spinal cord is an important factor in the production of the paralysis Little is known regarding the susceptibility to ischæmia of the cauda equina and anterior and posterior nerve roots, but it is probable that in this respect they resemble peripheral nerves rather than spinal cord Santemma (1946) suggests that ischæmia of the cauda equina is the principal cause of the neurological disturbances. He assumes that the blood supply of the cauda equina, like that of the peripheral nerves, is fundamentally regional and that an embolus at the aortic bifurcation which occludes the third and fourth pairs of

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* Welch (1910) states that in the majority of cases the last two pairs or only the last lumbar arteries are occluded In Case 13 in our series at embolectomy it was noted that there was vigorous pulsation in arteries anterior to and on both sides of the lower three lumbar vertebræ

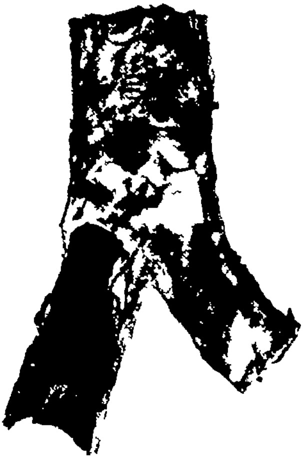

Fig. 36.—Aortic embolism. Case 12.—Posterior aspect of aortic bifurcation six months after embolectomy through the left common iliac artery.

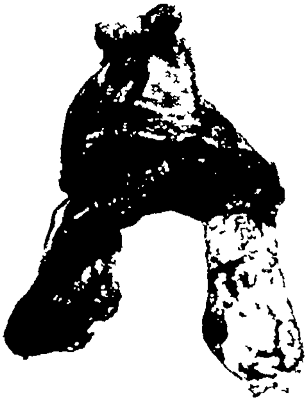

Fig. 37.—Aortic embolism. Case 12.—To show clot removed at aortic embolectomy. (Compare Fig. 36.)

lumbar arteries, the median sacral artery and its branches the fifth lumbar arteries, and prevents blood from reaching the cauda equina through the lateral sacral branches of the internal iliac arteries, will cause total ischæmia of the intraspinal nerve roots He further suggests that, if this hypothesis is correct, the level of sensory loss gives an indication of the height to which the embolus extends, for example a sensory level at the second lumbar dermatome indicates that the embolus has occluded the second pair of lumbar arteries Some of our observations lead us to think that ischæmia of the cauda equina or extraspinal nerve roots may occur in some cases of aortic embolism (Cases 11 and 13), but we believe that it is not the most important cause of the neurological disturbances

If the common iliac vessels and the fourth and fifth pairs of lumbar arteries are occluded either by clot or by spasm, then the lower limbs and the tissues of the buttock, lower back and lower abdominal wall will be partly deprived of blood That this happens in many cases of embolism of the aortic bifurcation is suggested by the experience that when the abdominal wall is incised little or no bleeding occurs The nerves running in these tissues will be ischæmic until such time as the collateral supply from above becomes efficient * It is not unreasonable to suppose that if this ischæmia lasts for one and a half hours, paralysis might extend as high as the inguinal ligament In their experiments on centripetal paralysis produced by compression of the arm with a sphygmomanometer cuff, Lewis *et al* (1931) found that after approximately thirty-five minutes the entire limb distal to the cuff was paralysed

If we accept the view that the initial symptoms do not indicate the moment of lodgement of the embolus but the moment at which the patient becomes aware of the effects of an ischæmia which has already been present for some time, then the time taken for paralysis to extend as high as the groins is even longer We therefore support the hypothesis that ischæmia of the lumbo-sacral plexus and of the peripheral nerves is the principal cause of the motor and sensory paralyses seen in cases of aortic embolism, and we consider that the rapidity with which the paralyses develop and their ultimate extent are indications of the degree of ischæmia which in turn depends upon the completeness of the obstruction of the bifurcation and the distribution of any reflex vasospasm

The development of muscle contractures marks the next stage in the evolution of the clinical picture We believe that the presence of contractures is evidence of a marked degree of muscle ischæmia and that, if they persist for more than a few hours, permanent damage to muscle is inevitable, thus even if complete sensory recovery occurs, the functional result may be impaired by fibrosis of the muscles In the early stages muscle contracture is reversible, for example, the disappearance of the contracture on the left side in Case 10 during spontaneous recovery and the rapid recovery observed in the contractures in Case 11 (right) and Case 12 (left) after embolectomy If there is hardening of the muscle and contracture of such a degree as to deform the joints, still the condition is not completely irreversible If the circulation is restored at this stage, the limb may be preserved although the functional result is unlikely to be completely satisfactory If the ischæmia persists the condition passes into the third stage with soft muscles, lax joints and swelling of the limb Motor recovery in the affected muscles is no longer possible and amputation may be inevitable It has not been sufficiently realised that the fate of an ischæmic limb may depend as much upon the state of the muscles as upon the state of the skin There is an obvious similarity between the stages through which the muscles of a completely ischæmic limb pass and the development of rigor mortis

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* Our clinical observations indicate that some time elapses before contributions from the superior epigastric and lower intercostal arteries are appreciable

Spontaneous recovery from embolism of the abdominal aorta is a rare event In their series of 193 cases, Albright and Leonard (1950) record 8 patients who recovered the use of the lower limbs without embolectomy Gesenius (1950) has since reported another case Data regarding several of these cases are incomplete and it is probable that some of them may have been similar to the 2 cases reported above in which there was " pseudo-embolism " of the aortic bifurcation

The number of successful cases of aortic embolectomy is now quite considerable Albright and Leonard (1950) have 26 in their series and their list does not include the cases reported by MacFarlane (1940), Agar (1943), Learmonth (1948, 3 cases *), Keeley (1948), Wilson (1949) and Ewing (1950, 2 cases) Since Albright and Leonard's review, another successful case has been reported by Taylor (1951) A study of the reports of many of these cases shows that, although the operation was successful in that the patient recovered and had good use of the lower limbs, in relatively few of the cases were restoration of circulation and recovery from the neurological manifestations immediate and complete This corresponds to our experience in the 4 successful cases in the present series

The explanation for the delay in the return of the circulation after a successful embolectomy is not immediately apparent It has been attributed to the persistence of arterial spasm (Nystrom, 1936), but this cannot be the whole explanation because the return of the pedal pulses is often delayed for weeks or even months (Table VIII) and indeed they have been reported as remaining absent permanently This suggests that organic occlusion of the main peripheral vessels has occurred and that when the pulse returns it does so through collateral vessels Such occlusion could be the result either of the lodgement of portions of embolus which have become separated from the main thrombus at the bifurcation and have been swept on to lodge in peripheral vessels, or of thrombosis occurring in the distal arteries during the period of ischæmia The former is a recognised danger of embolectomy and during the operation steps are taken to occlude the arteries immediately distal to the embolus so as to prevent fragments of the thrombus from being carried onwards This is likely to happen only when there is a rush of blood past the obstruction and therefore the danger is when the obstruction of the bifurcation is incomplete , it is possible that embolism of the peripheral arteries might occur while an incomplete block is becoming complete as well as during embolectomy In cases of *rheumatic heart disease with auricular fibrillation*, another factor which may explain the delay in the return of circulation is the presence of old emboli in the peripheral vessels , the presence or absence of the pedal pulses before the aortic occlusion is seldom known Case 15 in the present series illustrates two of these possibilities there were old emboli in the right external iliac and femoral arteries and a recent thrombus at the bifurcation of the left popliteal artery (Fig 29) Had this patient lived, the return of circulation to the legs could have been through collateral channels only Although the return of circulation may be delayed, this does not preclude an excellent functional result and, as our observations show, eventually the blood supply to the lower limbs may be more than adequate for all normal needs

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* Cases 11, 12 and 14 of the present series

Nor is neurological recovery immediate We have already considered *the development of the motor and sensory paralyses* and attributed them to ischæmia of extraspinal nervous pathways It follows that recovery of function depends upon restoration of blood supply to nerves It must be stressed that in our successful cases although the longest period before embolectomy was nine hours, this does not represent the longest period for which nerves were ischæmic Because of the slow return of circulation to the limbs, nerves, particularly those in the distal portions of the limbs, were ischæmic for much longer, probably for as long as forty-eight hours This is quite long enough to produce organic changes in peripheral nerves

The general pattern of recovery in the lower limbs is one of steady progression from above downwards , proximal muscles recover before distal muscles and the sensory level recedes distally Recovery proceeds at the same rate in both lower limbs In 2 of the cases in the present series (Cases 11 and 13), on one side there was a delay of more than twenty-four hours before function returned in the muscles below the knee The longest delay was fourteen days This period is too short to be accounted for by the processes of nerve degeneration and regeneration, and must be due either to a non-degenerative lesion of the nerves of ischæmic origin, or to the effects of ischæmia upon the muscles themselves The observations upon the small muscles of the feet suggest that in some cases complete denervation and re-innervation of these muscles may have occurred , thus the clinical picture indicates that the degree of ischæmic damage to nerves increases as they pass distally

Applied to the return of sensation, this hypothesis would lead to the expectation that if prolonged sensory disturbances were observed they should be of " stocking " or " sock " distribution, and that they should recover by gradual shrinkage towards the periphery This was precisely the type of sensory disturbance observed in the right leg in Case 14 (Fig 34)

The major sensory disturbances in Cases 11 and 13 were not of this type although in Case 12 at three months a " carpet-slipper " type of sensory disturbance was also present in the right foot When the residual neurological disturbances in these 2 cases are considered as a whole, we are forced to conclude that in both cases they suggest a root lesion (in Case 11 of lumbar 4 and 5, and in Case 13 of lumbar 3 and 4) rather than a peripheral nerve lesion The reasons why we consider it improbable that ischæmia of the spinal cord could be responsible for such lesions have already been discussed The lesions may be due to ischæmia affecting either the cauda equina or the lumbo-sacral plexus These structures are within the zone of ischæmia created by an occlusion at the aortic bifurcation and we have no means of telling how long they remain ischæmic Small fragments of an embolus entering one of the lumbar arteries, or the occlusion of the median sacral or lateral sacral arteries might account for serious lesions in these nerves

There is very little information in the literature of aortic embolism about the reflexes in the lower limbs Welch (1910) mentions that with complete paralysis the reflexes and electrical excitability are abolished Rothstein (1935) states that the reflexes vary , they may be diminished, normal or even increased *Our experience has been that the reflexes* are invariably diminished or absent Within as short a period as four hours after the initial symptoms both knee and ankle jerks may be lost After a successful embolectomy, return of the reflexes was slow and took longer than return of voluntary power in the muscles concerned (Tables XI and XII) When reflexes remained absent, there was always some weakness or loss of tone in the muscles concerned or else there was evidence of persisting nerve lesions For example, in Case 14 the absent right ankle jerk was associated with weakness of the dorsiflexors and plantar flexors of the foot and with a " stocking " area of sensory loss, and in Cases 11 and 13 the delayed return of the reflexes in the left and right lower limbs respectively was part of the residual neurological disturbances which have been discussed An absent or equivocal plantar response could be attributed either to weakness of the toe flexors or to diminished sensation on the sole of the foot, often with associated hyperpathia When the stimulus was applied, the foot was withdrawn but flexion of the great toe was absent With the recovery of sensation, a normal flexor response was obtained (Cases 11 and 13) On the other hand, ischæmia produces many bizarre effects and it may be that in these cases the explanation for the neurological disturbances is not simple but depends upon scattered lesions through the nerves of the lower limbs

When embolism at the aortic bifurcation is suspected, heparin should be given intravenously and if necessary morphine for pain The trunk and arms of the patient should be heated to about 40° C to encourage vasodilatation As a result of this treatment improvement in the neurological signs and reappearance of femoral pulses will occur in a proportion of cases in which the precipitating pathological process has been arterial spasm If improvement is absent after an hour or so, the heparin should be neutralised by an intravenous injection of protamine sulphate, and embolectomy should be performed We prefer the transperitoneal route , the exact site of the arteriotomy depends upon the appearance of the aorta and common iliac arteries We do not recommend the administration of heparin in the post-operative period

SUMMARY

1 The anatomical and pathological features of aortic occlusion are discussed

2 The clinical features of 11 cases of aortic thrombosis and 16 cases of sudden aortic occlusion are analysed

We have to thank those of our medical and surgical colleagues who permitted us to see and in some cases to treat certain of these patients

REFERENCES

AGAR, H (1943), *Brit Med Journ*, 2, 101 ALBRIGHT, H , and LEONARD, F C (1950), *New Engl Journ Med*, 242, 271 ALLIBERT (1828), Quoted by Welch (1910), HESSE (1921), and ROTHSTEIN (1935) ATLAS, L N (1942), *Surg Gynec Obstet*, 74, 236 BARTH, M (1935), *Arch Gen Med* (2nd series), 8, 26 BAUER, F (1913), *Zbl Chir*, 40, 1945 BULL, P (1922), *Acta Chir Scand*, 54, 315 CHIENE, J (1869), *Journ Anat Physiol*, 3, 65 DANZIS, M (1933), *Ann Surg*, 98, 249 DELANNOY, E (1945), Case reported by Leriche, R , *Mem Acad de Chir*, 71, 89 DENNY-BROWN, D , and PENNYBACKER, J B (1938), *Brain*, 61, 311 ELKIN, D C , and COOPER, F W (1949), *Ann Surg*, 130, 417 EWING, M R (1950), *Brit Journ Surg*, 38, 44 FANTONUS, J In Bonetus, T (1679), *Sepulchretum sive anatomica practica ex cadaveribus morbo dentatis*, Geneva GARVIN, C F (1941), *Amer Heart Journ*, 21, 713 GESENIUS, H (1950), *Zbl Gynakol*, 72, 257 GOLDSMITH, G A , and BROWN, G L (1935), *Amer Journ Med Sci*, 189, 819 GOODISSON, T (1818*a*), *Bull Fac Med Paris*, 6, 106 GOODISSON, T (1818*b*), *Dublin Hosp Rep*, 2, 193 GRAHAM, R (1814), *Med Chir Trans*, 5, 287 GREENFIELD, I (1943), *Ann Intern Med*, 19, 656 HAIMOVICI, H (1950), *Angiology*, 1, 20 HERTER, C A (1889), *Journ Nerv Ment Dis*, 14, 197 HESSE, E (1921), *Arch Klin Chir*, 115, 812 HOLDEN, W D (1946), *Arch Surg*, 53, 456 KEELEY, J L (1948), *Ann Surg*, 128, 257 LABEY, G In Mosny and Dumont (1911), *Bull Acad Med*, 66, 358 LEARMONTH, J R (1948), *Edin Med Journ*, 55, 449 LERICHE, R (1940), *Pr Med*, 48, 601 LERICHE, R (1946), *Thromboses Artérielles Physiologie Pathologique et Traitement Chirurgical*, Paris Masson et Cie LERICHE, R , and MOREL, A (1948), *Ann Surg*, 127, 193 LEWIS, T (1936*a*), *Clin Sci*, 2, 237 LEWIS, T (1936*b*), *Vascular Disorders of the Limbs*, London Macmillan & Co LEWIS, J , PICKERING, G W , and ROTHSCHILD, P (1931), *Heart*, 16, 1 LINDSTROM, B L (1950), *Acta Chir Scand*, 100, 367 MACFARLANE, J A (1940), *Brit Med Journ*, 1, 971 MCKECHNIE, R E and ALLEN, E V (1936), *Surg Gynec Obstet*, 63, 231 MADDEN, J L (1949), *Journ Amer Med Assoc*, 140, 760 MARTORELL, F (1946), *Accidentes Vasculares de los Membros*, 2nd edition, Barcelona Salvat Editores MAYCOCK, W D'A (1937), *Amer Heart Journ* , 13, 633 MILANES, B , STABLES, E P , and LASTRA, J S (1950), *Surgery*, 28, 684 MOORE, R M , and MOORE, R E (1933), *Amer Journ Physiol* , 104, 259 MOREL, A (1943), *Pr Med* , 51, 137 MURRAY, G (1943), *Surg Gynec Obstet* , 77, 157 NYSTROM, G (1936), *Lectures on Embolism and Other Surgical Subjects*, Baltimore Williams & Wilkins Co ORTNER, A B , and GRISWOLD, R A (1950), *Arch Surg* , 61, 793 PINKERTON, G E (1948), *Lancet*, 2, 811 PRICE, A H , and WAGNER, F B (1947), *Surg Gynec Obstet* , 84, 619 REICH, N E (1943), *Ann Intern Med* , 19, 36 REYNOLDS, J T and JIRKA, F T (1944), *Surgery*, 16, 485 RONALD, J , and LESLIE, M (1940), *Glas Med Journ* , 134, 7 ROTHSTEIN, J L (1935), *Amer Journ Dis Child* , 49, 1578 SANTEMMA, E E (1946), *N Y State Journ Med* , 46, 416 SEVERINUS, M A (1632), *De Recondita Abscessuum Natura*, Naples SHEPHERD, J T (1950), *Clin Sci* , 9, 49 STRAUS, R , DOMINQUEZ, R , and MERLISS, R (1946), *Amer Journ Med Sci* , 211, 421 DE TAKATS, G (1942), *Surg Clin N Amer* , 22, 199 TAYLOR, F W (1951), *Arch Surg* , 62, 38 TURNER, W (1863), *Brit For Med-Chir Rev* , 32, 322 WELCH, W H (1910), *A System of Medicine*, Ed by Sir Clifford Allbutt and H D Rolleston, London Macmillan & Co , vol VI, p 809 WILSON, H (1949), *Journ Amer Med Assoc* , 141, 389

TUBERCULOSIS AN INCIDENT OR A DISEASE?

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TUBERCULOSIS is not a disease of one tissue or organ, and I wish to discuss certain aspects of tuberculous infection and their influence on the forms which the disease may take and the course it may pursue These vary with periods of life and to a certain extent with the sexes at these periods I shall not touch on the vast problem of epidemiology except to remind you that its true appreciation demands the wide view of the trained sanitarian rather than the narrower view of the practising clinician Too close a focus on the individual may blind one to the more fundamental social and economic origins of the disease

IMMUNITY —Understanding of the problems of tuberculosis as it affects the individual demands a brief discussion of the pathology of infection and of immunity, for these are not merely problems of site and extent of disease but are bound up with states of immunity and allergy which ultimately determine the fate of the infected person We know that races exposed to tuberculosis for the first time show little power of resistance, and the classical instance of that was the fate of the Senegalese troops imported into France in the first world war and described so accurately by Borrel (1920) Between their almost complete inability to resist infection and the comparatively high resistance of Western races there is the intermediate state of the American negro race which in its passage through the tuberculosis epidemic is now showing evidence of developing resistance Western countries, highly industrialised and exposed to centuries of disease, have in the process of time, by the elimination of susceptibles, developed a high degree of immunity, and it is that inborn or natural immunity which forms the first barrier of defence in members of these communities

Although tuberculosis affects many animals, principally domesticated animals, its course is different from the disease in man, and many animals differ from man in their lack of resistance to the infection, a power which is highly developed in our race Infection in them pursues an inevitably fatal course characterised by widespread dissemination Infection in man pursues a similar course in exceptional circumstances only, for natural immunity places a check upon disease and initial infections are overcome by the majority In the minority the infection becomes firmly established and passes to disease which in some cases, which are exceptional in races of high resistance, leads to dissemination similar to that so often seen in animals

A Honyman Gillespie Lecture delivered on 11th October 1951

THE PRIMARY INFECTION —The first infection, whether it is held in check or advances, follows a characteristic pattern, that of the primary infection The pattern of this infection is well known—the small focus at the point of tissue entry, usually the lung substance, which tends to caseate rapidly and to heal, the rapid passage of the organism into the lymphatics and the swelling of the draining lymph glands It is this combination of primary focus and glands which constitutes the primary or Ranke complex The primary focus in the lung field is the so-called Ghon focus Primary complexes may form in fauces and neck glands, in intestine and mesenteric glands, in skin and regional glands In all, the glandular is usually, from the disease point of view, the presenting and predominating element

With extensive involvement of the lymphatic glands, particularly when the complex is in the lungs and the glands involved are mediastinal, intermittent passage into the blood stream of lymph cells carrying tubercle bacilli takes place and in this way, coincidently with the development of the complex, there is seeding of tubercles in other tissues and structures This is something quite different from the sudden eruption of a caseous focus which leads to acute miliary dissemination It is a silent process which may never declare itself, or may only do so months or even years later by a progressive focus in bone or joint, or genito-urinary tract, or lymph glands, or serous membranes During this phase sparse tubercle seeding of the lungs may also take place with apparent regression and even hyalinisation, and it is these seedings which are believed to play a part in the later development of ulcerative lung tuberculosis This period of primary and post-primary dissemination is the key to our understanding of many of the later phenomena of tuberculosis

The pattern of the primary infection is determined by the absence of tissue sensitivity That, as you know, develops about six or eight weeks after the infection—earlier if the infection has been heavy or repeated, later if the infection has been light With it comes that altered reactivity of the body to which v Pirquet gave the name of allergy, and then the body reactions change completely Tuberculous lesions developing after this period do so in tissues which react violently to the infection, and the characteristic of these lesions is the rapid tissue caseation and destruction There has been much controversy on the relationship of allergy to immunity and I do not propose in this talk to enter that controversial field There is little doubt that they are separate entities Immunological studies suggest that innate and acquired immunity rest on similar cellular foundations, and the ability of innate immunity to localise and heal the primary infection before allergy has developed is well known The rapid caseation and destruction of later lesions is the result of the allergic state of the tissues and it is easy to assume that the action of allergy is wholly deleterious, but the localising effect of allergy in subsequent infection and its destructive effect on the immobilised bacilli should be borne in mind

It develops along with acquired immunity and it may have potentialities for harm or for good It is certain that the two go together, and high degrees of immunity often, in clinical practice, go with high degrees of allergy

STAGES OF THE TUBERCULOUS INFECTION —In referring briefly to what is often termed Ranke's theory or Ranke's hypothesis, I do so not because it is accepted nowadays but because Ranke recognised certain stages of tuberculous disease and attempted to co-relate them with certain degrees of allergy His first stage covered the period of development of the primary complex and terminated with the appearance of allergy The second stage was said to be characterised by extreme degrees of tissue sensitivity, and Ranke related this to dissemination of the infection by lymph, blood, and tissue channels With a postulated waning of hypersensitivity the third stage of isolated phthisis was reached It is impossible to fit all tuberculosis into these convenient compartments and one certainly cannot relate the different disease phenomena so accurately to different degrees of allergy , but the theory is of service in calling attention to three definite periods of infection which, despite acknowledged variations, form a framework on which to build an understanding of the tuberculous process

It is not my intention to discuss in detail the primary infections The majority of these are silent They give rise to no symptoms and they are dealt with effectively by the forces of inborn immunity They produce no clinical signs and may show no radiographical evidence of their presence The conversion of the tuberculin reaction is the only proof that infection has taken place, but, however small the lesion may be it is believed that conversion will not take place unless tuberculous tissue has formed Many children live in contact with infectious adults and remain tuberculin-negative, and it is probable that their inborn immunity is sufficient to deal immediately with the tuberculous infection and prevent it from being implanted in the tissues Although we use the skin as an index of tissue sensitisation there is evidence that the skin is not always representative of body sensitisation Furthermore, allergy to tuberculous infection is not always elicited by tuberculin and it may require the employment of the whole bacillus (B C G) for its detection Even when the primary infection gives rise to gross lesions there is a high recovery rate and many lung complications of the glandular component resolve completely

When we talk of a dissemination phase of the primary infection we must remember that this may be of short or long duration, that the disseminations may be abortive, may declare themselves shortly after their implantation, or may do so only after a long interval Furthermore, there may be secondary disseminations from those sown at an earlier date Even with these limitations the conception of this phase is useful, for it is during it that the seeds of disease in tissues other than the lungs are sown There is also evidence that deposits sown in the lungs at this time may be responsible for later ulcerative disease of these organs

These extrapulmonary lesions form an interesting group, for, in the majority of cases, they are not associated with lung tuberculosis, and on the other hand lung tuberculosis in the majority of cases is clinically an isolated phenomenon and is not associated with disease of tissues which infection cannot reach by the tubular pathways It is, of course, by these pathways that the common complications of larynx and intestine arise

ALLERGIC PHENOMENA —It is in the early stages of the evolution of the primary infection that certain disease states commonly attributed to the allergy of the tissues arise, and the commonest of these are tuberculous rheumatism, certain conditions of the skin, principally erythema nodosum, and of the eye, principally phlyctenular conjunctivitis

Tuberculous Rheumatism —Tuberculous rheumatism has a long history and there is evidence that certain cases of chronic polyarthritis are of tuberculous origin, but that is not the type which is encountered in the early stages of the tuberculous infection Those who have taken many histories of tuberculous patients must have been struck, as I have been, with the frequency with which a previous history of rheumatic fever is given Yet these patients show no evidence of cardiac damage and the description of painful joints is not that of the inflamed intensely painful joints of acute rheumatism Sometimes the rheumatism appears to be in muscle or fibrous tissue but usually it is stated to have involved several joints, to have disappeared without treatment, and to have left no residual disability While similar attacks may occur during the course of an established tuberculous condition they occur usually before the tuberculosis has proclaimed itself and there seems to be little doubt that the condition is an allergic phenomenon. A similar arthritis often accompanies erythema nodosum which is accepted as having a similar ætiology and attacks of erythema nodosum may also occur during the course of established disease

Erythema Nodosum —The tuberculides are skin eruptions which are associated with tuberculosis of some other part of the body and they are now considered to be analogous to syphilides, trichophytides, etc , and to be caused by emboli of tubercle bacilli in the sensitised skin Erythema nodosum is not a true tuberculide and the tuberculides in fact do not occur during this early phase of the infection Although a majority of cases of erythema nodosum in this country is due to tuberculosis, an appreciable percentage is due to other causes, and the disease is best regarded as a syndrome caused by different allergens, bacterial or toxic The few recorded cases of finding of tubercle bacilli in the lesions are not fully authenticated When the syndrome is of tuberculous origin it almost always appears with the development of allergy, and this fact enables us to fix the primary infection at some period within the previous six to twelve weeks Instances of erythema nodosum of tuberculous origin recurring several times during the course of tuberculous disease, as I have already stated, are not uncommon

Phlyctenular kerato-conjunctivitis —Phlyctenular kerato-conjunctivitis also often makes its appearance during this period and it is considered to be an allergic phenomenon due, in the majority of cases, to tuberculous infection, but in a minority to other causes It differs from tuberculous rheumatism and erythema nodosum in running a more protracted course, for the phlyctenular masses ulcerate readily and infected ulcerative lesions often result It is mainly a disease of childhood and in many children the attacks recur There is obviously an underlying systemic cause and it is interesting that it manifests itself in this peculiar sensitivity of the superficial eye tissues Like erythema nodosum the lesion is met with more frequently in certain age groups The former occurs around, and in the early years of, puberty The latter occurs in childhood, and both appear to be commoner in Scandinavian lands Erythema nodosum has a much heavier incidence in females than in males It is not at all clear why these two tissues are involved so frequently in these phenomena It is known that some poisons, *e g* lead, involve certain tissues, and certain organisms and viruses have a similar tissue electivity Erythema nodosum and phlyctenular kerato-conjunctivitis develop during the primary tuberculous infection, the main element of which lies in glandular tissue, and it is believed by some (Brun and Viallier, 1948) that it is a specific product of the growth of tubercle bacilli in gland tissue which has this special affinity for skin and eye I shall come back to this theory later

POST-PRIMARY DISEASE —With the passage of this phase which is of uncertain duration and may never be detectable as a phase at all, the so-called post-primary phase is entered This phase by definition covers all tuberculosis which is not definitely a primary infection phenomenon and it may be said to cover the future life span of the tuberculous individual Many tuberculous lesions develop in the years which immediately follow the primary infection and it is useful to designate these as the early post-primary infection years In the earliest stages of this period, often in the first three months, appear *tuberculous meningitis* and *acute miliary disease* of young children, and within the first two years, very often within the first year, there appear the metastatic *bone and joint lesions* which are a common feature of the mid-childhood years and of adolescence These lesions are quite often multiple as one would expect in blood-borne conditions, and they may involve many tissues other than bones and joints Why some tissues like muscle escape completely—I have only once seen tuberculosis of skeletal muscle—and why others like thyroid are seldom affected is an interesting problem Even when only one bone or joint or viscus is involved clinically, disseminations into other areas have usually taken place, and the *bone marrow* is often invaded at a quite early stage of the dissemination period The involvement of this tissue in typhoid is well known, and sternal marrow puncture for purposes of culture (Hirsowitz and Cassel, 1951) has been employed. The use of this procedure in the diagnosis of disseminating tuberculosis yields positive results in an appreciable percentage of cases (Schleicher, 1946 , Horowitz and Gorelick, 1951) and is a useful diagnostic adjunct when diagnosis is in doubt

Pleurisy—Pleurisy with or without effusion appears in a preponderance of cases during the first year after the receipt of the primary infection Its exact pathogenesis is in dispute but its time of appearance and its significance should be recognised There are many points about this condition which are of great interest It is not often seen in childhood and the majority of cases occur between the ages of 15 and 25 There is no explanation of its rarity in childhood any more than there is of the rarity of ulcerative pulmonary tuberculosis in these years, and this is all the more interesting when one considers the fact of its intimate relation to the primary infection This fact links it with primary infection acquired in adolescence, but there is no agreement on the actual pathogenesis of the condition While some cases of tuberculous pleural effusion start insidiously, many have an abrupt onset with fever, pain in the side, and pneumonia-like symptoms, and one cannot escape the conclusion that the suddenness of the symptoms indicates an allergic reaction As by careful cultural examination tubercle bacilli can be found in a large percentage of the exudates, direct infection of the pleura by eruption of a caseous subpleural focus or of a caseous glandular focus seems likely Of greater interest is the future tuberculosis morbidity which is undoubtedly high, varying as it does in different series from 20 per cent to 40 per cent , and influenced probably by the care given to treatment at the time The most frequent subsequent lesion is tuberculosis of the lungs and this develops often within a year, and very often within two years, of the effusion The lung lesion may be of the typical so-called reinfection subclavicular type which leads to bronchogenic tuberculosis, or it may be of the bilateral apical type which leads so often to sluggish lung tuberculosis which remains so long confined to the upper lobes This type is probably of blood-borne origin The origin of the subclavicular infiltration is disputed, and it is worth remembering that when it develops it is not always on the side of the pleurisy Some effusions are followed by tuberculous lesions of bones, joints, kidneys, or other extra-pulmonary tissues, and there is general agreement that pleurisy is an early manifestation of tuberculous infection which may terminate in pulmonary or extra-pulmonary disease

Tuberculosis of extra-pulmonary tissues is common in childhood during the years when ulcerative tuberculosis of the lungs is rare , but it is also common in the early years of adult life when this type of lung tuberculosis is frequently encountered and is, in fact, responsible for a very high mortality While it is true that extra-pulmonary tuberculous lesions are not commonly associated with progressive lung tuberculosis and while the converse is also generally true, the facts hold good in a clinical rather than in an anatomical sense Nevertheless, from the behaviour of the tissues involved the two types of disease are different clinical entities For all that, pulmonary tuberculous lesions are fairly common accompaniments of extra-pulmonary tuberculosis (Mann, 1946, Hawkins and Thomas, 1946, Marienfeld, 1938, Pagel, 1938) but in children the pulmonary disease is practically always the primary lesion from which the hæmatogenous spread occurred, and in adults it is of a type which suggests a blood-borne origin and clinically shows a greater tendency to healing than does ulcerative bronchogenic tuberculosis The latter does, however, occur Pleurisy can thus be a precursor of blood-borne disease of extra-pulmonary tissues or of two clinically different types of lung tuberculosis Even if the pathogenesis of the re-infection type, subclavicular in site, is unknown, we must grant that it too may be a hæmatogenous lesion In support of this is the fact that while the majority of lung lesions which accompany blood-borne extra-pulmonary tuberculosis are bilateral and of similar origin as judged by their distribution and radiographical appearances, an appreciable number conform to the re-infection type of lesion and behave as such (Marienfeld, 1938, Pagel, 1938) Post-primary tuberculosis can thus be of two distinct types which are partly determined by age, but they show a considerable degree of overlapping as some of the lung lesions which accompany bone and joint or other blood-borne diseases are of the bronchogenic type even when they are later developments Furthermore, in a fairly high percentage of cases of chronic lung tuberculosis blood-borne lesions of other tissues develop They may not present clinical symptoms during life but they are easily detected post-mortem (Willis and Rosenthal, 1945)

Chronic Disseminated Tuberculosis—There is a type of tuberculosis, usually met with in young adults, lasting often for a large number of years, and characterised by the development of successive lesions in various extra-pulmonary tissues Many of these cases start with pleurisy and the lesions may involve joints, bones, serous membranes, glands, soft tissues, skin, and genito-urinary tract Very often the lungs also are involved in a hæmatogenous type of disease Each lesion leads as a rule to rapid initial destruction of tissue and when healing appears to be in progress it is followed by a new lesion in some other site The disease lasts over many years and cure is possible It is for this type of disease that the term "chronic disseminated tuberculosis" suggested by Pagel should be reserved The lesions in this type of disease probably come from a central lymphatic focus and the disease is characterised by high tissue sensitivity The healing of the lesions suggests the building up of local tissue immunity and the repetition of the disseminations suggests a low state of general immunity This conception of local tissue immunity explains many puzzling clinical manifestations of tuberculosis In chronic ulcerative pulmonary tuberculosis, as I have already stated, disseminations are common, but clinical disease in other tissues or organs is rare, and it may be that the type which post-primary tuberculosis will take is determined in the first instance by the general and local tissue immunity of the individual In adult life the common pattern of disease is isolated tuberculosis of the lungs

Genito-urinary Tuberculosis—Tuberculosis of the genito-urinary tract is a blood-borne manifestation and it may involve the components of the tract singly or in combination It is a not infrequent complication of chronic pulmonary tuberculosis, the kidney being involved in about 8 per cent of all fatal cases and the genital tract in about 10 per cent of fatal cases in men and 5 per cent in women The incidence in non-fatal lung disease is certainly less Renal involvement is very common in the chronic disseminated type of tuberculosis which I have discussed, but it is often a silent condition and is detected comparatively late in the disease When it occurs as a solitary clinical tuberculous manifestation it appears in relation to the primary tuberculous infection at a much later date than bone and joint tuberculosis This fact has been discussed by Ustvedt (1947) and Ustvedt and Wergeland (1949) who point out that an interval of more than ten years separated the two conditions in a large percentage of a series of cases which they were able to follow from the time of the primary infection There is little doubt that the kidney infection is sown during the early dissemination phase and that the development of the disease to a stage when symptoms are produced is relatively slow. The frequency of kidney involvement in patients suffering from non-pulmonary tuberculosis was pointed out by Medlar (1926) and is well known clinically to those who have been interested in this type of disease Band and Munro, quoted by Munro (1944), found an incidence of tubercle bacilluria in 21 6 per cent of 300 cases of pulmonary tuberculosis, and in serial sections of 33 pairs of kidneys from these patients found giant cell systems in the cortex in every instance Munro (1944) found a similar incidence of kidney involvement in children passing through a primary tuberculous infection and recorded the presence of tubercle bacilluria in 19 per cent of 188 such children, a minority of whom had grave tuberculous lesions Only four died and he was able to secure three pairs of kidneys None showed any naked eye evidence of tuberculosis but in all serial sections showed bilateral tuberculous lesions, usually more advanced in one kidney These positive findings are very much higher than the incidence of clinical renal tuberculosis and demonstrate the frequency of renal involvement and also the frequency of its healing The clinical incidence of renal tuberculosis in patients suffering from pulmonary tuberculosis does not exceed 5 per cent

Tuberculosis of the Skin—I have referred already to the question of local tissue immunity and to the greater resistance of certain tissues to tuberculous infection The tuberculosis physician, and by that I mean the physician who handles all types of tuberculosis, sees little of tuberculosis of the skin That is partly because skin lesions are referred to the dermatologist, but apart from that the development of tuberculous skin lesions in patients under his daily care is not frequent With the exception of the *scrofuloderma* group in which the skin is infected from underlying tuberculous disease or adjacent mucous membrane tuberculosis, and of the rare cases of direct infection of the skin, all skin lesions are of blood borne type The commonest is *lupus vulgaris* and this may involve multiple areas of the face, trunk, and limbs, although it occurs with greatest frequency on the face and in the nose This group represents true tuberculosis of the skin Scrofuloderma and lupus arising from underlying lymph gland tuberculosis, are of course, of local origin, but much lupus is of hæmatogenous origin The *tuberculides*, unlike true skin tuberculosis, are evanescent phenomena Although tubercle bacilli have been found in the lesions of all of the group—*lichen scrofulosorum*, *papulo-necrotic tuberculides*, and *erythema induratum*—they are regarded as eruptions produced by the action of emboli of tubercle bacilli on allergic skin They usually occur in young adults or children and while there may be a history of tuberculosis or concomitant tuberculosis of bones, joints, glands, etc, very often the patient comes, or is brought, for advice on account of the skin eruption Although the tuberculides are obviously blood borne deposits they are not common They may appear at any time in the course of the disease or after the date of infection and, apart from erythema induratum and papulo-necrotic tuberculides of the extremities in which circulatory stasis may be a predisposing cause, it is usually impossible to say what determines their appearance They are practically never seen in patients who are ill from tuberculosis and they are associated with mild types of tuberculosis and a good general condition It is interesting that lupus is very often an isolated phenomenon, and if there is associated tuberculous disease it is, as a rule, benign It is established (Rich, 1944) that tubercle bacilli can become attenuated in the skin, but this does not altogether explain the comparative rarity of tuberculides and tuberculosis of the skin, or the infrequency of their association with other forms of active tuberculosis

Tuberculosis of Lymph Glands—If we exclude the disseminated tuberculosis of lymph glands which is a common feature of progressive tuberculosis of primitive races and is rarely seen in races with greater inborn resistance to tuberculosis, lymph gland tuberculosis in this country is usually the glandular component of a primary complex It has been my experience that children who recover from extensive glandular tuberculosis, whether of cervical, mediastinal, or abdominal origin, very rarely develop further manifestations of tuberculosis at a later period Clinical experience should not be the foundation of dogma, but the experience of the Frenchman Marfan that those who had suffered from tuberculous cervical adenitis which had healed before adolescence rarely developed pulmonary tuberculosis, has become exalted to a law which is still spoken of as *Marfan's law* Nothing is absolute in Medicine, but clinically this observation holds true. In the skin we have a tissue which seems to have a high natural resistance to tuberculosis but which paradoxically seems to be involved when general resistance to tuberculosis is high The lymph glands bear the brunt of primary tuberculous infection in childhood, and recovery seems to lead to a high degree of acquired resistance (Wilkinson and Curetin, 1943) against subsequent tuberculous disease.

The ability of tubercle bacilli to survive for long periods in lymph gland tissue is well known, and in fact one of the theories of the much disputed origin of pulmonary tuberculosis is founded on this fact. These theories ignore the anomaly of organisms living an apparently saprophytic existence in one tissue and producing disease in another, but if we grant the possibility of varying degrees of local tissue immunity there need be no difficulty in accepting them No one with any real knowledge of tuberculosis believes that the state of allergy of any one tissue is representative of that of the body as a whole, but it is a new conception that the action of the growth of tubercle bacilli on different tissues may produce different allergens which have a selective action on different tissue systems of the body

Tuberculosis of the Abdomen—It is doubtful whether one is justified in including in this condition the ulcerative lesions of the bowel which complicate a large percentage of cases of pulmonary tuberculosis The commonest abdominal tuberculous lesions are of primary origin, basically glandular in type, with varying degrees and types of peritoneal involvement and many of them are due to bovine infection The peritoneum may be involved in the multiple serosal involvement which occurs as a post-primary blood borne phenomenon and it is often picked out by acute miliary tuberculous disease The localised hyperplastic forms which involve principally the terminal ileum and cæcum, and occasionally the distal colon, form an interesting group They are rarely associated with other obvious tuberculous lesions and they conform pathologically to a primary type of infection

Tuberculosis of the Eye—Tuberculous lesions of the eye have always presented a difficult problem Some are of bacillary origin and their pathogenesis and pathology are not in dispute Others—and these include the vast majority of cases (Duke-Elder, 1939)—whether it be keratitis, scleritis, iritis, choroiditis, retinitis, etc, present a non-descript non-specific clinical and pathological picture and their relation to tuberculosis may be deductive or even inferential These lesions may be equally attributable to non-tuberculous disease in different areas of the body, but they are often associated with occult tuberculosis, usually of lymph glands It is difficult to understand why the tissues of the eye should be affected by distant tuberculous foci which appear to be innocuous to the rest of the body and it is believed (Duke-Elder, 1939) that the essential factor in these common inflammations is a hyper-sensitive or allergic state of the ocular tissues themselves I have already stated that the sensitivity of the skin is not a true index of the sensitivity of other tissues It is well known to those who have experience of tuberculosis in its many manifestations that certain types of tuberculosis, particularly tuberculosis of peripheral glands which have undergone caseation, give rise to very high degrees of skin sensitivity, and some tissues, for reasons which we do not understand, may acquire greater sensitivity than others There is very often a family tendency to particular manifestations such as those in skin and eye, and repeated exposure of these tissues to the allergens increases their sensitivity "It is thus" states Brun (1949), "that successive reinfections in one segment of the eye end by creating a state of local susceptibility, latent and chronic, a veritable fire which smoulders under the embers of a focus which is never extinguished and which anything may fan into flame"

Tuberculous eye lesions are not common and are seldom seen with active pulmonary tuberculosis , but they are not infrequently associated with healed tuberculosis of the lungs or with infection of the lymphatic glands, particularly those of the lung roots (Duke-Elder, 1940) This author concludes that, with the exception of acute miliary tuberculosis, tuberculosis of the eye "occurs with the greatest rarity in the presence of active tuberculosis elsewhere but rather in apparently normal healthy well-nourished individuals with a healed or benign tuberculous infection in some organ, usually the lymphatic system in the chest, more rarely in the lungs, the glandular depot, even although it is usually slight, quiescent, clinically healed or calcified, being capable of disseminating infection after the primary pulmonary focus has healed, presumably by the occurrence of an intermittent bacillæmia which is usually without systemic significance" Brun (1949) makes an almost similar statement and emphasises that when tuberculosis of the eye does develop with lung tuberculosis it is usually after the lung disease has healed He states that these lesions are practically always associated with foci of tuberculosis in glands and that the eye manifestations are a late development of infection The gland foci themselves are often old and latent and the same is true of visceral foci when these are present He claims that the allergens are a specific product of the growth of tubercle bacilli in gland tissue and that they have an elective action on mesenchymal tissue Eye tuberculous lesions are to him a mark of immunity against progressive lung tuberculosis The two conditions develop in entirely different soils, and it is there that we see the explanation of the apparent antagonism which exists between lesions of skin, glands, and eye on the one hand and lung tuberculosis on the other The latter disease is also entirely different from the chronic disseminated tuberculosis which I have discussed Perhaps at the other extreme where anergy is the rule lies sarcoidosis, and it is interesting that the soil which favours these particular non-pulmonary tuberculous states can be influenced by diet (Cameron, 1951) and very often by calciferol. Both appear to affect the background of the disease and in this way modify its course.

Chronic Pulmonary Tuberculosis.—The principal tuberculous lesion, the one which constitutes our main social and therapeutic problem, is tuberculosis of the lungs. No satisfactory explanation has been given of why this condition is so rare in childhood and why it appears so suddenly and with such frequency in young adult life to become, as it were, the pattern of adult tuberculosis. It is to a very large extent a one organ disease and we can understand the involvement of that organ when we reflect that the majority of tuberculous infections are acquired by inhalation and that the lung capillaries constitute a filter for all venous blood and are likely to arrest tubercle bacilli which have entered the circulation from lesions elsewhere. The cavity formation characteristic of allergic tissue, and the spread by the air passages to other areas of the affected organ or its neighbour, are also understandable. It is not a disease which as a rule is associated with high cutaneous allergy and, except in its terminal phases, it is not marked by blood dissemination although these disseminations do take place. They rarely, however, progress to disease, and tissue resistance including that of the lung itself is obviously high. It is this resistance which makes it amenable to surgical methods of treatment which overcome mechanical obstacles to healing and it is this resistance which, reinforced by good conditions of hygiene and diet, by itself can finally effect cure. I have already discussed the apparent antagonism between chronic lung tuberculosis and other types and forms of tuberculosis and I have stated that there are differences in the human soil in which these various types flourish. If we say that they thrive in varying humoral states we are no more specific, but it is an interesting fact that they are types each of which seems to follow a definite course. We do not know why lung tuberculosis appears so suddenly at puberty or why it tails off at the end of the sexual life of the female and is prolonged into, and even intensified in, a later period of male life. The procreative life of the male covers a wider span than that of the female and this type of lung disease does seem to be associated with that period of life. It is extremely sensitive to social, economic, and nutritional factors, but it remains the type of tuberculosis of adult life.

There is growing evidence that pulmonary tuberculosis is in many cases intimately related to the primary infection, particularly when that infection is acquired in early adult life, and then it appears often within two years and very often within five of its establishment. Other cases develop at periods which are more remote from the infection. In the one we see the efflorescence of the seed. In the other we suspect that a new sowing has taken place. So we have the *endogenous and* *exogenous theories*, both of which are true The localisation of the disease to the upper areas of the lungs is probably dependent on the dynamics of the pulmonary circulation (Dock, 1946, 1947) and is not a point which I shall discuss here Neither shall I discuss the problems of tuberculous meningitis which formed the subject of a recent lecture

I have tried in this talk to fit into a clinical picture the ramifications of tuberculosis in the human body, to present them as parts of one pathological process, and to integrate them with varying degrees of resistance of the tissues of the individual What I have discussed are essentially clinical problems, but tuberculosis has wider issues While it is possible to draw a fairly composite picture of the disease, many things remain which we do not understand The title has asked a question—is it incident or disease, the incident in the individual or the repercussions on the community? A narrow outlook and a restricted interest in Medicine may focus interest on solitary incidents in the individual to the exclusion of the disease itself A wide outlook on the problems of disease and a catholic interest in Medicine take us into problems of greater issue to the individual and the community Tuberculosis is fundamentally an incident in the individual and a disease in the community It has many facets and it is not capable of solution by slogans or formulæ It admits of no solitary answer, for behind it those with understanding see social and economic issues which must be faced before the disease and its incidents can be eliminated The soil of the individual influences the incident The soil of the community influences the disease, and it is there that our greatest problem lies

REFERENCES

BORREL, A (1920), *Ann Inst Pasteur* 34 105
BRUN, J (1940), *Rev de la Tub* 13, 34
BRUN, J, and VIALLIER, J (1948) *Rev de la Tub*, 12 385
CAMERON, C (1951), *Lancet*, 1, 807
DOCK, W (1946), *Amer R Tub*, 53 207
DOCK, W (1947), *Radiology*, 48, 310
DUKE-ELDER, W S (1939), *Textbook of Ophthalmology*, 2, 1485
DUKE-ELDER, W S (1940), *Textbook of Ophthalmology*, 3 2287
HIRSOWITZ, L, and CASSEL, R (1951) *Brit Med Journ* 1 862
HOROWITZ, R and GORELICK, D F (1951), *Amer R Tub* 63 346
MARIENFELD, O (1938), *Papworth Res Bull* 37
MEDLAR, E M (1926), *Amer Journ Path*, 2, 5
MUNRO, W T (1944), *Edin Med Journ* 51, 101
PAGEL, W (1938), *Papworth Res Bull* 57
RICH, A R (1944), *The Pathogenesis of Tuberculosis*, 92, 640
TUFTS, L (1936) *Journ Immunol*, 21 85
USTVEDT, H J (1947), *Tubercle*, 28 22
USTVEDT H J, and WERGELAND H (1940), *Act Tub Scand* 23 26
WILKINSON, M C, and CURETIN R I R (1943) *Lancet* 2 662
WILLIS, R A, and ROSENTHAL, D B (1945), *Med Journ Austral*, 2 30

OBITUARY

Dr ROBERT DURWARD CLARKSON

By the death of Dr Robert Durward Clarkson, former superintendent of the Royal National Institution for the Mentally Defective at Larbert, on 6th November 1951, Scotland lost a distinguished Physician and Psychiatrist, and one of the foremost authorities on Mental Deficiency

A scholarly man and one of outstanding ability, he had a distinguished career at Edinburgh University graduating B Sc in 1866 at the age of nineteen and M B , C M four years later In 1906 he obtained the degree of Doctor of Medicine, his thesis for that degree being on "Mental Deficiency," and in 1910 his Fellowship of the Royal College of Physicians of Edinburgh After graduating he occupied various hospital posts, including the Edinburgh Royal Infirmary and the Sick Children's Hospital, where he was closely associated with the late Dr John Thomson, working with him in his clinic for mentally defective infants and young children He then took up general practice in Falkirk where he was in very truth "The Beloved Physician" and was appointed visiting medical officer to the Royal Scottish National Institution in 1895 In 1911 he became resident medical superintendent, a post he occupied till he retired in 1935

His thoughts and interests were early turned to mental deficiency when, as a boy, holidaying in the country he found the defective son of a farmer tied up in a byre for his own safety His talks with the boy and the sympathy aroused made a deep impression on him, an impression which remained with him all his life Dr Clarkson's knowledge of mental deficiency and his understanding of the defective were in advance of his times At the time he entered the Institution, little was known about Mental Deficiency The Royal Commission had not issued its report There were no Mental Deficiency Acts At that time the general public took the view that nothing could be done for defectives and that permanent custodial care was necessary for their own safety and that of the community Dr Clarkson at once took up the cudgels on their behalf, declaring emphatically that the well educated, trained and understood mental defective could become socially efficient and an asset rather than a liability

At that time, too, the I Q was unknown, yet Dr Clarkson could diagnose and assess with a skill and accuracy unsurpassed to-day

He spoke on many platforms and expressed his opinions with a forcefulness and earnestness which carried conviction He proceeded to put his views into practice and very soon had an excellent Special School established within the Institution and also developed training facilities for older patients His great desire was to have a separate colony for adults, and this was achieved in 1934 The colony, situated in beautiful surroundings, now stands, a worthy memorial to his foresight and vision

Dr Clarkson was one of the founder members of the Scottish Association for Mental Health There his advice and help were invaluable and were eagerly sought and freely given, not only in matters pertaining to mental deficiency, but also in the wider field of mental health A man of deep religious convictions, he stressed the great importance of religion in the field of mental health and of bringing the churches into it On a number of occasions he gave evidence on behalf of the Association to Governmental Committees, notably the Committee on Protection and Training, the Russell Committee and the Committee on the Scottish Health Services He also represented the Association at the Second International Congress on Mental Health in Paris in 1936

He went to live in Perthshire on retirement, but remained consultant to the Institution and the Stirling Infirmary, served on various Medical Boards and continued to take an active interest in the work of the Voluntary Association During the war years he and his family kept open house for serving men and women from overseas Two hundred and thirty-eight took advantage of this, some returning on every leave They came from Canada, New Zealand, Australia, South Africa, France, Belgium, Holland, Norway, Poland, U S A and two from the Argentine, and many grateful letters from the boys and girls so far from home showed how much this was appreciated

Throughout his life he kept an open mind, always ready to listen and pay attention to the views of others A man of great charm and ability, he was of a retiring disposition and simple tastes who sought neither publicity nor position, but merely to serve others By his love, sympathy and understanding he brought happiness and a new hope to the lives of so many This was very evident by the number of his old patients who later visited him, some to seek further advice and guidance, and all to thank him

As one of his children said of him—" His was the humility of the truly great He gave us, his children, eyes to see with, which we could never hope to use with his patience and perception But what a legacy ! What a trust ! "

Those of us who had the privilege of knowing him and of working with him feel that he has left to us also a great trust

NEW BOOKS

Electroencephalography in Clinical Practice By R S SCHWAB, M D Pp 195, with 106 illustrations London W B Saunders 1951 Price 32s 6d

This book is addressed to "neurologists, internists, psychiatrists and neurosurgeons" rather than to electroencephalographers It is surprising, therefore, to find that only three of the nine chapters deal specifically with use of the E E G in disease and that whilst there are eleven half-tone blocks illustrating different types of electrode and electrode holders, epilepsy is dismissed in 23 pages One of the figures (p 92, Fig 63) is said to be the electro-encephalogram of a case of "severe epilepsy" with "clinical evidence of deterioration" but the record corresponds closely to the pattern seen in subacute progressive encephalitis Surface electrodes were first used by Adrian and not by Gibbs as the author states The text appears to have been hurriedly written, a phrase such as "drawing his attention olfactorily to the smell" should have been recast The book is well produced and it is useful to have Dr Schwab's numerous contributions to electroencephalography summarised

Management of Celiac Disease By SIDNEY V HAAS, M D, and MERRILL P HAAS, M D Pp 188, 15 illustrations London Lippencott 1951 Price 40s net

This is an excellent book, most of its pages being devoted to a review of literature There are 668 references The etiology of the condition, which is frequently familial, is quite unknown, but the authors think that there is some mechanism in the intestinal tract whereby polysaccharides are converted into substances that irritate this tract Diagnosis may be difficult, and perhaps fibrosis of the pancreasd is not a separate condition but due to severe cœliac disease Treatment should be chiefly dietetic and the authors claim excellent results in 370 cases treated with a diet consisting at first of banana, protein milk, meat and cheese as a basis Under such a regime recovery should be complete with no relapses, no deaths, no crises and no stunting of growth

Chronic Bronchitis By TREVOR HOWELL, M R C P ED Pp viii+111, with 3 plates London Butterworth & Co (Publishers) Ltd 1951 Price 17s 6d

This is an essentially practical book by an author with much experience of the problems of chronic bronchitis in geriatric practice The ætiology, pathology and symptomatology are fully discussed before going on to the actual management of the patient Full details are given of controlled experiments with expectorant drugs, and their usefulness is questioned Greater success may be expected from the proper employment of antispasmodics and antibiotics with a place for physiotherapy It is emphasised that each case must be looked upon as a separate problem This easily read book may be thoroughly recommended

Dianetics By L R HUBBARD Pp xvii+413 London Derricke Ridgway 1951 *Price 30s net*

This shamelessly pretentious book, subtitled "The Modern Science of Mental Health," is a contribution not to science but to mumbo-jumbo Orthodox psychiatry is abused and in its place is introduced "The Hubbard Dianetic Foundation Inc," with the discoveries of "the single source of mental derangement," and "a therapeutic technique with which can be treated all inorganic mental ills and all organic psychosomatic ills, with assurance of complete cure in unselected cases" What is new in Dianetics is mostly nonsense, and rather dangerous nonsense An extraordinary transatlantic mixture of sophistication and ingenuousness, it is of interest only as a pathological cultural symptom

Clinical Unipolar Electrocardiography By B S LIPMAN and E MASSIE Pp 232 with 191 illustrations Chicago The Year Book Publishers 1951 Price $5

In 135 pages of text this book gives a straightforward explanation of the unipolar lead patterns commonly encountered in clinical practice The arrhythmias are not considered The principles of electrocardiographic interpretation are based on the pioneer work of both Wilson and Goldberger, explanations are clear and balanced

The liability to error in basing a diagnosis of ventricular hypertrophy on the voltage of the QRS complexes alone, the importance of serial electrocardiograms in diagnosing obscure myocardial infarction, indications for additional leads, the changes associated with potassium and calcium serum levels are all carefully explained

There are 63 pages of illustrative electrocardiograms at the end of the book They suffer from the faults of the direct-writing electrocardiograph employed, but are reasonably clear The legends are the least satisfactory part of the book, hypertrophy is repeatedly referred to as enlargement and the explanations are not always clear or satisfactory

At $5 this useful little book is expensive for the British reader

Diabetes Control By EDWARD L BORTZ, M D London Henry Kimpton 1951 Price 25s

This book is written as a guide for the diabetic patient Every aspect of diabetes is considered including early detection, causal factors, psychology of the diabetic, life insurance and dietetic and insulin treatment The rules which the diabetic must follow are discussed in detail, with perhaps rather too much repetition

The explanation of diet planning seems unnecessarily involved There are thirty pages devoted to meal planning The recipes and foods suggested are, of course, American and in many cases are not available in this country

While there is much of value in this book, the average patient might find it rather beyond his requirements

The Genetics of Micro organisms By D G CATCHESIDE Pp 223, with 49 tables and 35 figures London Sir Isaac Pitman & Sons 1951 Price 21s net

Since Pasteur's use of a micro organism in the preparation of isomers, Leeuwenhoek's "anamicules" have become increasingly popular as a convenient form of guinea pig The basic sciences owe much recent advance to studies of these lowly forms of life which possess considerable advantages from a research point of view for instance with some species of fungi, all the products of any one meiosis may be recovered with ease and studied individually

The author has based his text on lectures to biochemists specialising in microbiology but the book will provide fodder for all those interested in the innermost secrets of tissue cells—from the problem of cancer to evolutionary theory

Doctors by Themselves By EDWARD F GRIFFITH, M R C S, L R C P Pp xxii+614, with 16 plates London Cassell & Co 1951 Price 21s net

This is a medical anthology containing over 800 short extracts from the writings of medical men ancient and modern The book is a wonderful miscellany on all kinds of subjects and offers a great variety of interest The extracts have been collected under five principal headings—the doctor at work, the doctor amuses himself, the doctor's troubles, the doctor looks at life, and lastly life, death and immortality, and each of these has been further subdivided so that kindred subjects are gathered together Individually, the writings are of the most varied nature There is the polite note of William Withering declining an invitation to duel, John McCrae's notes on Flanders battles, Hippocrates on sterility, Dawson's classification of the middle aged, James Lind on the scurvy, Jenner on the songs of birds and many others A most interesting and valuable collection, a wonderful bedside book and a relaxation for the leisure moment

NEW EDITIONS

Immunology By N P SHERWOOD, PH D, M D, F A C P Third Edition Pp 731, with 8 coloured plates and 21 line drawings London Henry Kimpton 1951 Price 56s net

As in previous editions the text is written mainly for medical undergraduates but also for all those interested in immunity from a philosophical point of view New chapters on special subjects such as Rh factors and venereal diseases will be of interest to hospital laboratory workers As in previous editions, emphasis is laid on the practical aspect of diagnostic laboratory tests

Discussion throughout the book deals with the underlying principles involved in infection and resistance and includes changing points of view with regard to immunity, recent ideas about vitamins, endocrines, the mechanisms of viral infection, latent infection and the new blood group factors

The chapter on flocculation tests in the diagnosis of syphilis has been rewritten by Frank Victor and includes references to the recent work of Kahn, Kline and others The serology of syphilis has been brought into line with the procedure details in J A Kolmer's recent publications

The Practice of Endocrinology Second Edition, Edited by RAYMOND GREENE Pp xxiii+389, with 56 illustrations London Eyre & Spottiswoode 1951 Price 65s

Dr Greene and his colleagues are to be congratulated on the appearance of a second edition of their excellent contribution to the *Practitioner* series within three years of its first publication The new edition contains further illustrations of high quality and a clear and concise chapter on Diseases of Adaptation It has been revised and brought well up to date There is no better book for the general practitioner, or the general physician, who requires an accurate, readable and intelligent guide to modern clinical endocrinology

X-ray Interpretation By H CECIL H BULL, M A, M B, M R C P Second Edition Pp xxxiv+406, with 287 illustrations London Oxford University Press 1951 Price 25s net

A second edition of this volume on X-ray interpretation appears after an interval of sixteen years It is doubtful whether such a small work as this can cover satisfactorily so wide a field as radiology presents to day Moreover, it would appear that the limited space available has not been employed to the best advantage, so that important subjects receive but scant consideration There are no reproductions of radiographs, these being replaced by line drawings, and there are so many inaccurate or misleading statements in the text that the book cannot be recommended

Cunningham's Textbook of Anatomy Ninth Edition, Edited by J C BRASH, M C, M A, M D, D SC, F R C S E Pp xx+1604, with 1252 figures, many in colour and 58 plates London Oxford University Press 1951 Price 90s net

The first edition of this work appeared in 1902 and the last in 1943 Since then numerous changes have occurred which have necessitated the introduction of several contributors who fully maintain the tradition of the work

The present edition has been very fully revised both as to text and illustrations with the addition of the latest discoveries in various departments This is particularly true of embryology where the material is enriched by recent researches on very early human embryos At the end of each section a fully representative bibliography is included The production of the book, the printing and the reproduction of the illustrations are of the highest standard This popular textbook will continue to merit the confidence placed in its predecessors as the leading authority in the language

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BCG-VACCINATION AS A PUBLIC HEALTH MEASURE

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BEFORE entering into my main subject, BCG-vaccination as a public health measure, it may be desirable to say a few introductory words about this vaccination. Probably at least a part of my audience has only rather vague ideas about this procedure as this kind of measure is new in Scotland.

The vaccine contains BCG-bacilli, named from the initials of the inventors, Calmette and Guerin. These BCG-bacilli are a living but avirulent strain of bovine tubercle bacilli. In experiments on animals it has been shown that inoculation of BCG produces tuberculin sensitivity and increased specific resistance to virulent superinfections. Applied in an adequate way they produce tuberculin sensitivity also in man after a reasonable lapse of time, and follow-up studies of groups of vaccinated and non-vaccinated people have shown a significant reduction of tuberculosis morbidity and mortality in the vaccinated group. I will refer to these experiences later. The vaccination is without danger and is accompanied only by small local inconveniences. With the method mostly used, the intradermal inoculation, a papule arises after some weeks at the site of injection. It increases slowly to pea-size and may sometimes show small pustule formation. This abscess heals spontaneously after a couple of weeks and leaves a whitish scar. The regional glands may increase somewhat in size, but only exceptionally is there lymphadenitis of any significance.

Some very important principles must be followed in the practical performance of BCG-vaccination. Firstly, only those who are still tuberculin negative should be vaccinated; those who are tuberculin positive after tuberculous infection have already acquired through this infection the increased resistance that the BCG-vaccination should confer. Every individual who is going to be vaccinated should be tested with tuberculin in order to exclude a virulent infection. Negative

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The Frederick Price Lecture delivered at the Royal College of Physicians, Edinburgh, 16th October 1951.

tests occurring after exposure should be retested six to eight weeks later and only if the test is still negative should the inoculation be made If this rule is not followed there is a great risk that recently acquired *primoinfection may manifest itself before the BCG-immunity* is effective The vaccination in such cases has been of no value and may be misinterpreted as the cause of the tuberculous disease, or doubt may be cast on the efficacy of the vaccination

Secondly, the vaccination should be performed in such a manner that tuberculin sensitivity arises If tuberculin sensitivity is not checked after inoculation there is no proof that the vaccination has taken and immunity been produced It is assumed that there is probably no immunity established until the vaccination has produced a systemic reaction that may be demonstrated by a positive tuberculin test In order to avoid misinterpretations and misjudgment of the efficacy of the inoculation, exposure should therefore be prevented during this pre-immune period

These are the principles that have been followed since BCG-vaccination was introduced in Sweden a quarter of a century ago The same principles have been followed in the other Scandinavian countries They have been followed also in the mass campaign against tuberculosis in the war-devastated countries in Europe and undeveloped states outside Europe In this Joint Enterprise of the Scandinavian countries, WHO and UNICEF, about 17,000,000 persons were vaccinated Experience with the practical performance of BCG-vaccination under various conditions is thus very great

What can be expected from the prophylactic effect of the vaccination ? From a theoretical point of view one ought to expect the same *kind of immunising effect as results from a well tolerated virulent* tuberculous infection The latter produces a specific resistance against superinfections It is very seldom that superinfection in a tuberculin positive individual causes any harm BCG-immunity is without doubt weaker than that which follows a virulent infection and it may be more easily overcome The immunity makes itself shown even in such cases, however, by diminishing the pathological effect of the virulent infection , it is seldom that we see a severe clinical primary tuberculosis in those who have acquired BCG-immunity before infection

The immediate pathological effect of a virulent infection is thus in high degree neutralised by the BCG-immunity This immediate consequence includes not only primary tuberculosis, but also miliary tuberculosis and tuberculous meningitis, and both these malignant tuberculous diseases may to a very great extent be prevented by *BCG-vaccination In none of the Scandinavian countries has a case of these malignant disseminated forms of tuberculous disease been* seen in an adequately vaccinated person

According to reports from several quarters, post-primary pulmonary tuberculosis arises more frequently in persons with marked primary tuberculosis than in persons who show insignificant or no reaction in the lungs after airborne virulent primary infection Because BCG-vaccination to a great extent prevents severe primary tuberculosis it is possible that it also diminishes the risk of acquiring post-primary pulmonary tuberculosis later As will be seen from the slides that I will show in a few minutes theoretical speculation corresponds to practical experience

In summary it may be said that an adequately performed BCG-vaccination produces specific immunity that is sufficiently strong to protect to a great extent against severe primary tuberculosis, miliary tuberculosis and tuberculous meningitis and to a certain extent, also, against pleurisy and post-primary pulmonary tuberculosis The morbidity and mortality rates of tuberculosis have been at a marked lower level in all reports of follow-up studies of adequately vaccinated groups of people as compared with tuberculin negative non-vaccinated groups It may be said, however, about most of these studies, that the way in which they were performed is not above criticism, and the conclusions drawn have not always been correct The reliability of the results can not therefore always be taken for granted I will only quote a few of the more recent and, according to my judgment, more reliable studies

The first report of the effect of the vaccination in school-children in the Swedish antituberculosis campaign in Rhineland-Westphalen in Germany (1948-49) has just been published Out of 1 1 million tuberculin-negative children, 400,000 were vaccinated, while in 700,000 the offered vaccination was not accepted Only 5 children in the vaccinated group fell ill with tuberculosis = 0 012 per thousand, and only 3 of them contracted tuberculous meningitis, = 0 007 per thousand The corresponding figures in the non-vaccinated group are 131, = 0 187 per thousand, and 71, = 0 101 per thousand The conclusion drawn is that the incidence of tuberculous disease is about 15 times greater in the non-vaccinated group (Fig 1)

I may refer to Dr Tornell's report from a small Swedish town as an example of the value of BCG-vaccination in combating tuberculosis in a community Of those who had been exposed to tuberculous infection after the establishment of the BCG-immunity, 8 2 cases in each 1000 years of observation contracted tuberculous diseases, while of the non-vaccinated exposed tuberculin-negatives there were 136 cases for each 1000 years of observation (Fig 2)

The results of the vaccination in the Swedish army, reported by Difs and Dahlstrom, are very interesting In 1941-44 25,239 tuberculin-negative conscripts were vaccinated and 36,235 remained un-vaccinated One must remember that the sources of infection were not immediately eliminated at the beginning of the military service and that those vaccinated might have been exposed to virulent infection during the incubation period of BCG, as it takes about six weeks for the vaccination to be effective and about the same time for the tuberculous infection to manifest itself, the full effect of the protection could not

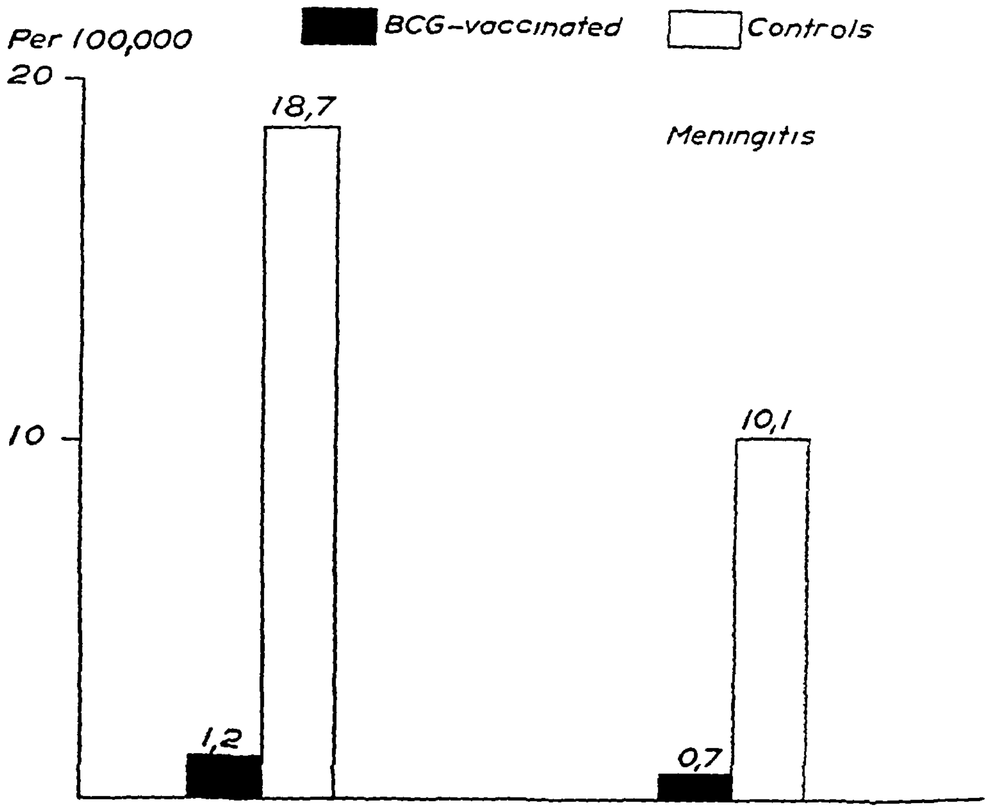

FIG 1 —Germany Disease in 400,000 BCG vaccinated and 700,000 Non vaccinated School children

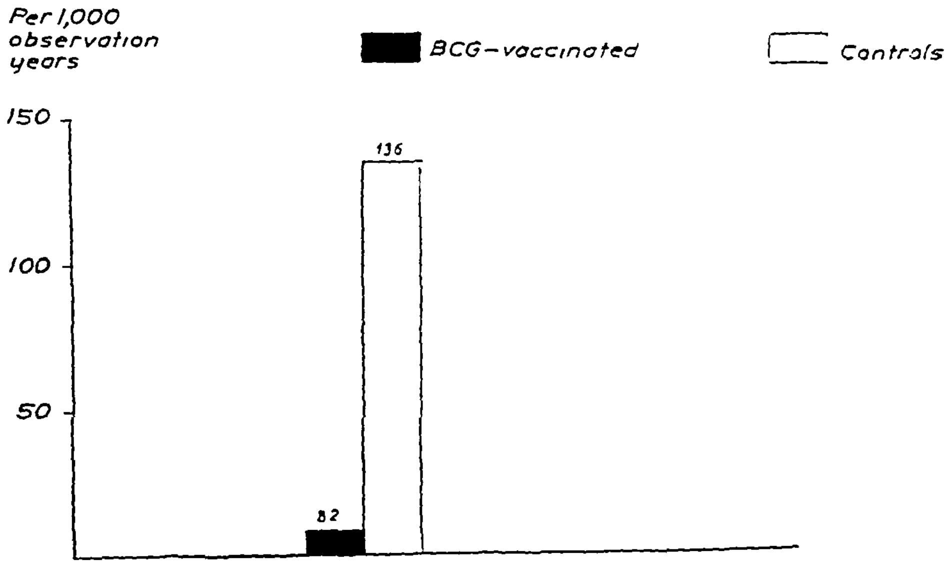

FIG 2 —Sweden Tuberculous Disease in BCG vaccinated and Non vaccinated Groups of the Population (Tornell) per 1000 Observation years

be expected until after three months (Fig 3) At a follow-up study in 1946 the following incidence of different kinds of tuberculosis were found —

Number of months after vaccination		0 2	2 4	4 6	6 8	8 10	10 12	more than 12
Primary tuberculosis	Vaccinated	27	14	2	4	1	5	5
	Non vaccinated	34	22	15	19	10	13	27
Pleurisy	Vaccinated	6	13	19	7	9	5	17
	Non vaccinated	3	12	8	22	6	19	45
Destr pulm tub	Vaccinated	3	0	1	0	0	0	5
	Non vaccinated	1	0	1	0	4	1	19

The experience of the Danish school-physician Hyge has often been quoted because the conditions correspond closely to those of a laboratory experiment The 12-18 year-old children were tested with tuberculin and the non-reactors (200) were offered BCG-vaccination One hundred and six accepted the vaccination During two months the children were exposed to accidental tuberculous infection from a deputy teacher, and the effect of the ensuing epidemic was reported by Hyge three years later Two of the 106 BCG-vaccinated girls had mild pulmonary tuberculosis and 41 of the 94 non-vaccinated tuberculin negative girls acquired tuberculous diseases , 6 of them had to be treated by pneumothorax and 1 of them died The morbidity rates were 1 9 and 43 6 per cent respectively In the spontaneously tuberculin positive group the rate also was 1 9 (Fig 4)

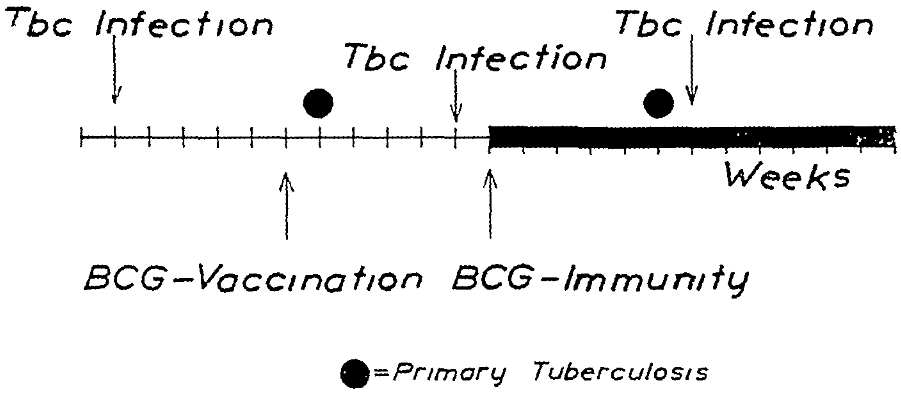

FIG 3

Since 1926 Heimbeck has vaccinated pupil nurses on a voluntary basis in Oslo In 1948 he checked the morbidity and the mortality rate in the two groups of vaccinated (501) and non-vaccinated (284) tuberculin negative nurses In the first group the morbidity rate was 9 9 and the mortality 1 0 per 1000 observation years, compared to 41 4 and 4 7 respectively among the unvaccinated (Fig 5)

The experience of Aronson and Palmer in the U S A is perhaps of

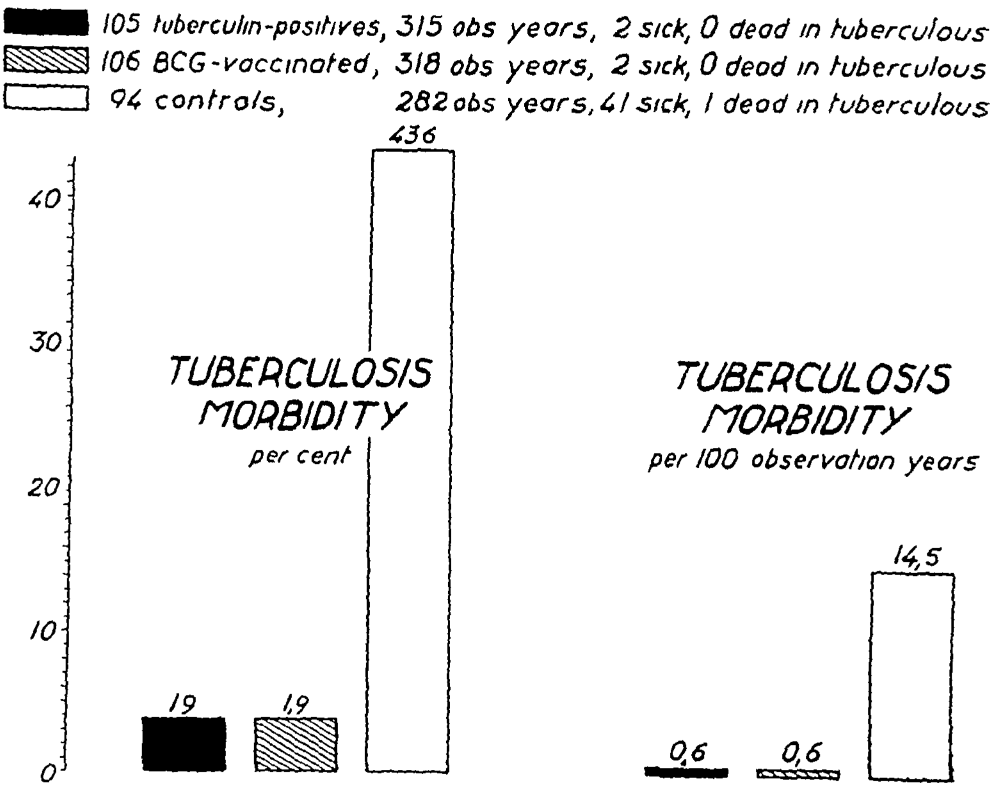

FIG 4 —Hyge 1947 (Highschool—Girls)

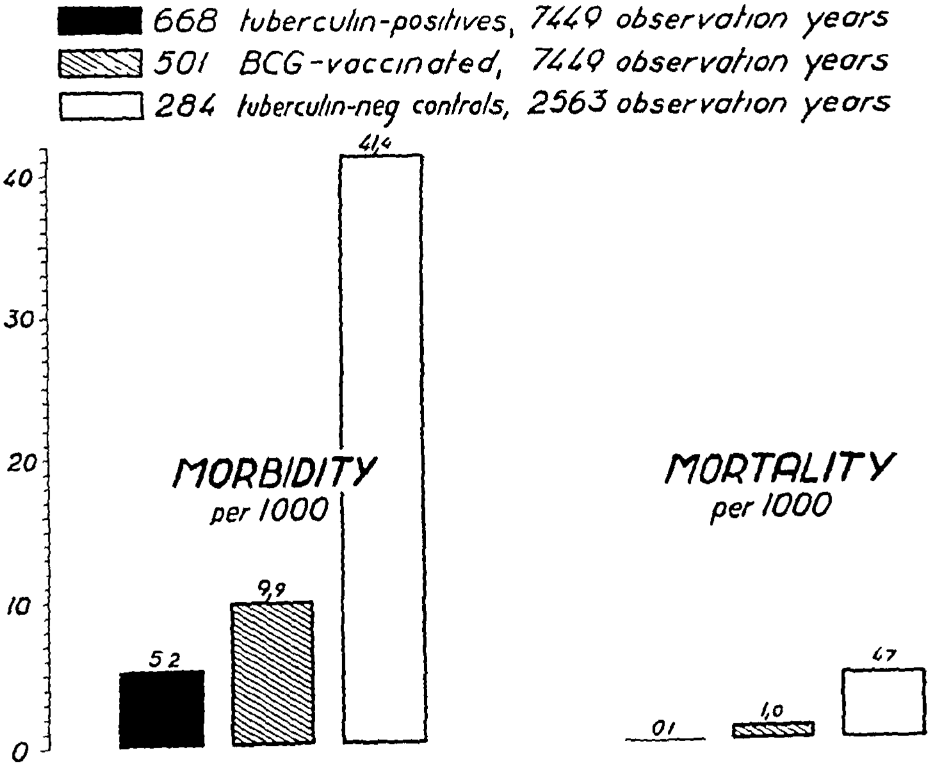

FIG 5 —Heimbeck 1948 (Pupil nurses)

special interest from a public health point of view In 1935-38 they tuberculin-tested Indians aged 1-20 years on several reservations and found 3000 non-reactors They injected BCG in half of this group and saline solution in the rest In 1948 a follow-up-study showed that the morbidity rate in the vaccinated group was 40 or 0 4 per 1000 observation years and 185 = 3 4 per 1000 observation years in the non-vaccinated group (Fig 6)

In none of the hitherto reported follow-up studies has the incidence of tuberculosis been equal or less in a non-vaccinated group Most

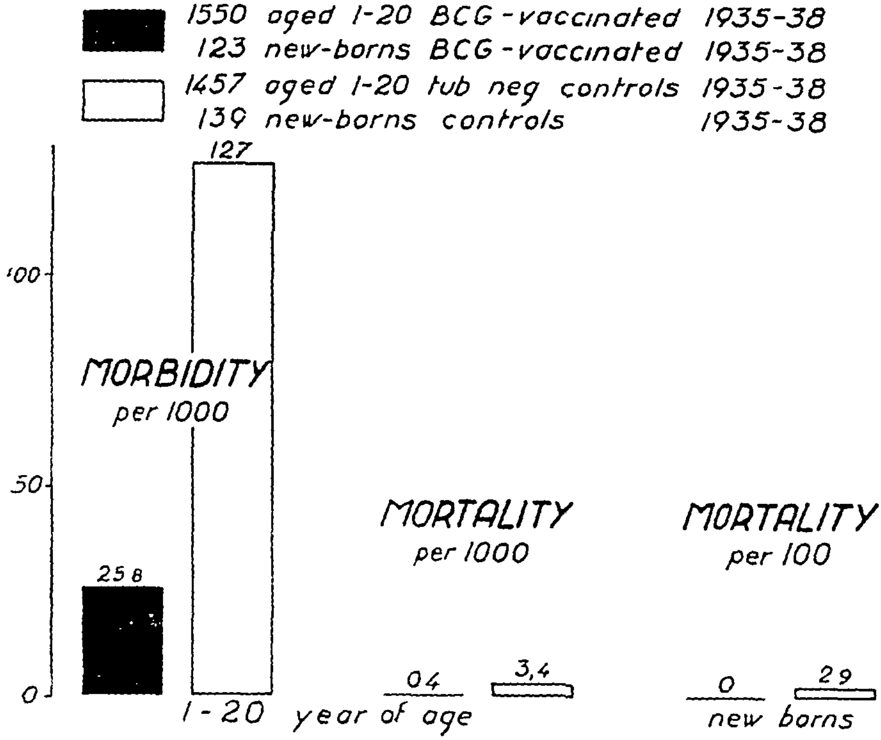

FIG 6—Aronson 1948 (Indians)

observers are therefore of the opinion that BCG-vaccination has proved its immunising effect and ought to be accepted as public health measure against tuberculosis

If the health authorities in a country intend to introduce BCG-vaccination as a means of combating tuberculosis the question may arise if this should be done on a voluntary or compulsory basis When other used and accepted measures are compulsory, for example notification of new cases, examination of family contacts, pasteurisation of market milk, why should not BCG-vaccination also be made compulsory ? As a matter of fact this has been done in some countries, among others Norway, France, Yugoslavia and Turkey Most public health authorities have, however, kept BCG-vaccination on a voluntary basis, while trying to educate the public to accept it The effect of

BCG-vaccination as a public health measure cannot be compared to that of smallpox vaccination and its value is still disputed in some quarters

The experience of a quarter of a century has shown that BCG-vaccination is quite without danger However, the inconvenience of the abscesses that are produced exceptionally and never can be prevented with absolute certainty would probably be exaggerated if they occurred in an individual who did not want to be vaccinated The effect of vaccination could be misinterpreted and counter propaganda might be started This is especially true in west-democratic countries in which the population is accustomed to make its free choice in most matters In these countries enlightenment and propaganda ought to be sufficient and give satisfactory support to BCG-vaccination If the effects of the vaccination are as striking as they have been in the Scandinavian countries, there ought to be no difficulty in persuading threatened people to have themselves vaccinated

The relativity of the protection that a BCG-vaccination affords also makes the introduction of compulsory BCG-vaccination in the public health scheme undesirable Even the immediate pathological effects of primary infection cannot be prevented with certainty, and protection against the very important late post-primary forms of tuberculous disease is still less certain Reluctant people cannot be told that if they have their children vaccinated it will keep them free from tuberculosis Against the spread of tuberculous infection in a community BCG-vaccination is of small immediate effect as the primary tuberculous disease that may arise in unvaccinated persons seldom constitutes a source of infection For the sick individual and his family the sickness is a tragedy, but from a public health point of view it is of less immediate importance

One must also always weigh the degree of risk that a person runs against the nature of measures to be taken against this risk The risk depends on two different factors the danger of infection and the possibility of the infection becoming dangerous The risk of infection must in general be regarded as very small in a community with low tuberculous morbidity and mortality In such a community there are few ambulatory sources of infection and therefore small danger of becoming infected Out of 1000 tuberculin negative individuals perhaps only one will acquire the infection annually One must unnecessarily vaccinate 999 persons in order to give relative protection to 1

In a community with a high tuberculous morbidity, with numerous sources of infection, many of which cannot be controlled by the public health service because they are still undetected, the risk of tuberculous infection will be very great Out of 1000 such persons of such a community perhaps 500 will be infected within a couple of years Vaccination of tuberculin negative persons gives obvious results and the gain in health of the population more than compensates for the time and trouble spent on vaccination In communities that from a tuberculous prevalence point of view occupy an intermediate position between the mentioned two extremes, the risk varies with the degree of tuberculous morbidity, and with it the necessity of BCG-vaccination This is true for most communities

The risk of infection is, of course, not equal for every member of the community The degree of the risk depends on the environment in which the individual lives or works—whether or not there are any sources of infection which cannot be avoided Tuberculin negative members of tuberculous families and medical and nursing personnel in hospitals where consumptives are treated are probably the groups most threatened with being infected in the near future These groups need every kind of protection and they ought to be the first to be BCG-vaccinated in a community that intends to introduce this method in its public health service scheme There are some other groups that are more or less on the same level as the above-mentioned in regard to the degree of risk of infection, dentists, personnel in shops, banks and post offices, *i e* people who in their profession must come in close contact with many people, among whom there may be consumptives

From quite another point of view those engaged in certain other occupations constitute groups for whom an improved protection against tuberculous infection is especially desirable those belonging to the military forces and the crews of cargo and passenger ships The risk of being infected may not be greater than in the population in general, but the consequences of primary infection, sickness and loss of working capacity, may be of much greater immediate importance When these groups fall ill and become bed-ridden they cannot be immediately replaced If many soldiers in a division acquire tuberculous disease and have to be at least temporarily discharged from the military service the effective force of the division is decreased If many able seamen or firemen of a merchant ship's crew fall ill, the ship may be too short of hands to manœuvre satisfactorily It would therefore be prudent to prevent or to lessen the sickness hazard by BCG-vaccinating those who are tuberculin-negative at the beginning of the military service or when enlisting as members of a ship's crew There are other professions in which it may prove especially difficult to get competent deputies in the event of sickness, for instance, teachers

Another factor is also to be considered when it is a question of vaccination on a voluntary basis namely the degree of facility and convenience in performing the vaccination The necessary preparation and examinations before and after inoculation, tuberculin testings, segregation of the person to be vaccinated, if necessary, and the inoculation itself, demand many visits Under certain circumstances this inconvenience is minimised, namely when the individual to be vaccinated, is hospitalised or otherwise kept under continuous medical control

This is the case with new-born babies in maternity hospitals, school children, conscripts and children living in various kinds of child institutions The newborn babies at the lying-in hospitals are seen daily by the nurses and/or doctors and it causes very little trouble to inoculate them Pre-vaccination tuberculin testing is not necessary In countries where most deliveries take place in maternity hospitals the first BCG-vaccination is more and more often performed in the newborn babies In Stockholm, for instance, children are only exceptionally born at home More than 90 per cent of all newborns are BCG-vaccinated at the maternities It is easy to perform the necessary tuberculin control of the vaccinated infants if they are regularly supervised by a welfare centre The tuberculin tests can be performed there and read by the nurse during home visits

In all progressive countries school children are regularly controlled by the school health services In some countries tuberculin testing is routinely made on school children It is an easy task to inoculate the tuberculin negative ones with BCG and to control the BCG-vaccination by new tests some months later In our country tuberculin testing is performed at least twice during the school years, once when the child starts school at 7 and then when he is ready to leave school at 15 years of age In connection with this tuberculin testing those who are still negative are offered BCG-vaccination The parents are informed about the value of BCG-vaccination, their consent to perform the vaccination is requested, and usually is readily given It is especially important to give the increased resistance that a BCG-vaccination can afford to a tuberculin negative adolescent, who is about to leave school and perhaps also his parents' home in order to continue his studies elsewhere or to learn a profession He may move from an almost tuberculosis free community to a city with a high incidence of tuberculosis The exposure risk in the new environment, over which the parents have no control, may be much greater than in the old one In addition, there is increased susceptibility to the more severe forms of primary tuberculosis at this age

Conscripts are examined when they start military service, and their state of health is continually supervised by medical officers Tuberculin testing and microradiography of the chest should be constituents of the medical examination It is an easy task to inoculate BCG in the non-reactors and to test if the vaccination has taken afterwards In our country this has been in effect since 1940 and at present more than 50 per cent of the non-reactors accept the vaccination Partly due to their susceptible age, partly to the change of environment and the hard military training, the conscripts probably run a greater risk of being infected and of acquiring a more severe form of tuberculosis than the population in general Especially in the beginning, before the group has been duly examined and those who are sick excluded from service, some of the reactors may suffer from hitherto unknown and undetected destructive pulmonary tuberculosis These conscripts constitute dangerous sources of infection for their tuberculin negative mates As has already been stressed, there may be some cases of tuberculous disease manifested among the vaccinated non-reactors within the first two to three months of the military service, because the immunity is not established until six to eight weeks after the inoculation Therefore the rational thing to do is to vaccinate the future conscripts before enlistment in order to provide them with the increased resistance offered by BCG-vaccination

All hospitalised patients, for example expectant mothers in the maternities, and children in children's hospitals, as well as all inmates of institutions, such as children in day-nurseries and play-schools, are subject to medical control Tuberculin testing and BCG-inoculation in those who are non-reactors can easily be performed at the visit of the physician or the visit of the child

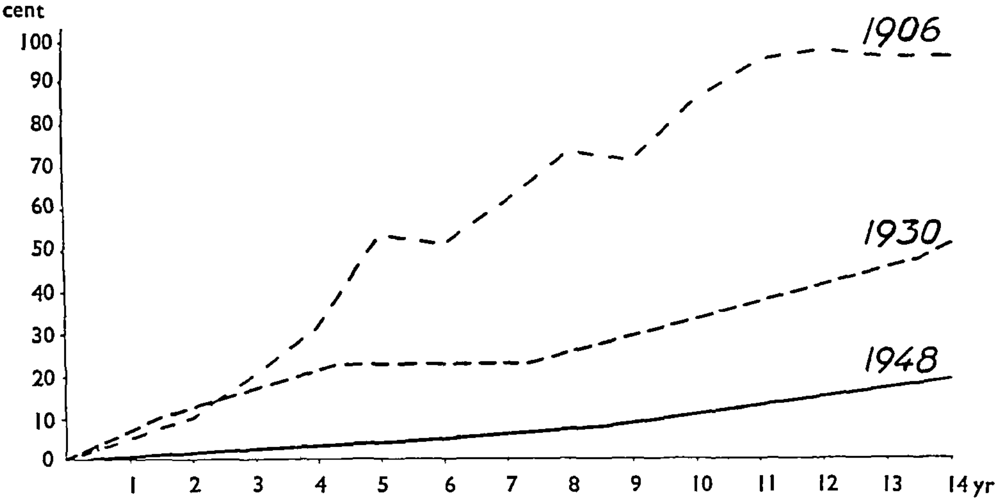

FIG 7 —Incidence of Tuberculosis Infection in Childhood

The degree of the risk of primary infection also depends on the susceptibility of the individual which varies a great deal It is, for instance, different in varying age groups as is shown by this diagram (Fig 7) The direct pathological lesions of primary infection are usually benign It is only exceptionally that the most common type of primary tuberculosis, that in the lungs, progresses to a fatal termination Other localisations of primary tuberculosis seem to be still more benign Death from primary tuberculosis is as a rule due to acute disseminated forms of the disease, miliary tuberculosis and tuberculous meningitis The mortality rate of primary tuberculosis reflects thus the incidence of the latter two tuberculous diseases, this holds true even to-day with the improved prognosis due to streptomycin treatment

From the mortality rate in different age groups it can be seen that the worst prognosis of primary infection is in infants and young children The mortality rate then declines and reaches its lowest point at about 10 years of age and later increases somewhat at puberty (Fig 8) Now the mortality curve does not indicate the degree of danger of a primary infection in different age groups unless it is contrasted with the incidence curve of the infection This well-known curve shows that very few infants are infected and that the incidence increases slowly and reaches its peak at about 40-45 years of age Thus, at an age with the smallest number of infected, the number of those dead with primary tuberculosis is highest, and at an age with about 100 per cent infected the mortality rate is almost nil This must mean that the younger the child the more dangerous is the primary infection, and that the danger increases somewhat again at the age of puberty The figures of the percentages may vary from one country to another, but the trend of the mortality and type of the infection incidence curves is the same everywhere From this one may conclude that the most susceptible individuals in the population are infants, small children and young people at puberty From a public health point of view it should be regarded as important to diminish the greater risk of tuberculous infection these age groups run by increasing their resistance This can be accomplished by BCG-vaccination

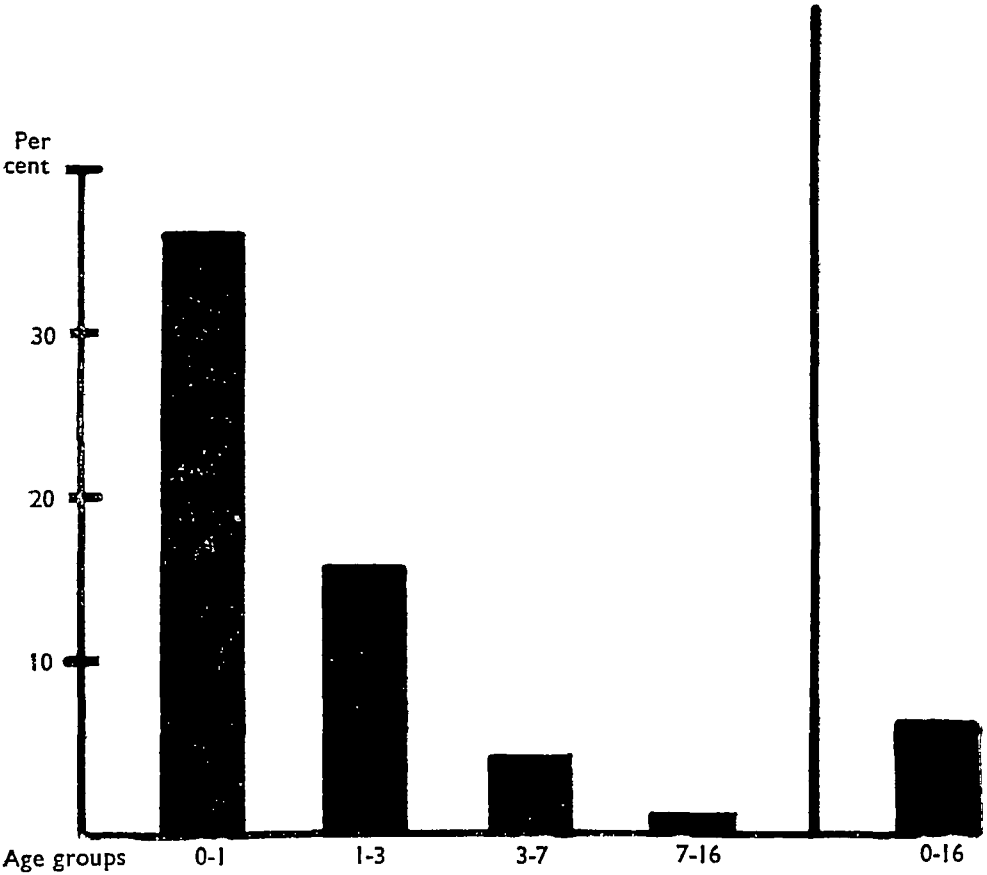

FIG 8 —Mortality Rate from Tuberculosis in different age groups

Now the importance of primary tuberculosis cannot be evaluated solely on the basis of the mortality curve The morbidity also plays a significant role This seems to be neglected or at least underrated by some authors Nobody knows the exact incidence of clinical primary tuberculous disease after the first infection, but the morbidity is of course much higher than the mortality In our own experience the *morbidity is apparently greater in the youngest age groups than in* the oldest ones It is rare for an infant or very small child to escape a clinical primary tuberculosis after infection, and it is rather unusual for an individual at 30-40 years of age to fall ill with this disease after having acquired the first infection The only possible way to get information about the morbidity rate is to follow the fate of non-reactors until they have acquired their first infection and then to examine them carefully by X-rays, temperature measuring, sedimentation test, gastric lavage test, etc , in order to find out the immediate consequences of the first infection

If one judges from reports, the incidence of clinical primary tuberculosis seems to vary considerably in different countries In Central Europe and the Scandinavian States it is a very common disease, while in some North American states, for instance, Minnesota, it is a very rare illness It is only in countries where primary tuberculosis is frequent that it becomes a public health problem

Even if primary tuberculosis in adults is not dangerous, it is nevertheless of importance because its manifestation means loss of *working capacity for some months with resultant loss of income,* social consequences, etc It is evident that it is of interest not only for the family but also for the community to prevent these sequelæ of a primary infection in individuals of professional age In school children and university or vocational students it may mean loss of study capacity and difficulty in keeping up with the teaching programme

The duration of the effect of a public health measure is of great importance , it must not be too temporary In this respect the duration of BCG-immunity is of great interest So far our knowledge about this matter is rather poor It is difficult to study this question because we have no reliable test on immunity in human beings In practice we use the tuberculin test to judge whether BCG-vaccination has been effective or not, but this is not a reliable test of immunity as sensitivity to tuberculin and specific resistance to tuberculosis are not identical , one can exist without the other and they do not necessarily run parallel Tuberculin tests are, however, the only means of telling if BCG-vaccination has led to the expected general change of mode of reaction in the inoculated individual From experiments on animals with inoculation of living tubercle or BCG-bacilli it is known that the tuberculin sensitivity is demonstrable about the same time as immunity In practice we consider a person immune to tuberculous infection if he is tuberculin positive and we apply the same test when it is the question of BCG-vaccinated persons This is, however, an assumption and may be wrong in exceptional cases

Another factor that makes it very difficult to determine the duration of BCG-immunity is the ever-present possibility of virulent superinfection When a BCG-vaccinated person acquires a primary tuberculous infection this does not as a rule produce any immediate clinical signs, partly, at least, thanks to BCG-immunity The virulent superinfection produces in its turn specific tuberculosis immunity, which is doubtless far stronger and more durable than immunity after BCG-vaccination The weak BCG-immunity has thus been transformed into a strong specific tuberculosis immunity If one tests such an individual with tuberculin it is not BCG-immunity but naturally acquired tuberculosis immunity that is tested Now most people in a community live in environments such that the occurrence of accidental virulent infection cannot be excluded with certainty

There are no reliable means of differentiating the tuberculin sensitivity produced solely by BCG-vaccination from that produced by virulent superinfection Usually sensitivty is much stronger after virulent infection, but the sensitivity after BCG-inoculation sometimes becomes gradually very marked Probably most students of this question agree with Herzberg's opinion that a sudden increase in tuberculin sensitivity, that remained low for a long time after BCG-inoculation, indicates the occurrence of a virulent superinfection It is not often that one has the opportunity to control tuberculin sensitivity after BCG-vaccination with sufficient frequency and regularity to aid in elucidating the problem of the duration of BCG immunity Usually we cannot determine whether or not a virulent superinfection has occurred We consider all BCG-vaccinated persons who are still tuberculin positive as being BCG-immune, unless it is obvious that they have been exposed to and acquired a virulent infection In general, this judgment ought to apply, but single cases may be misinterpreted The evaluation of the duration of BCG-immunity by tuberculin tests must therefore be accepted with some reserve as a method used only because we lack other more reliable tests

Experience has shown that the duration of tuberculin sensitivity after BCG-vaccination, in people evidently not exposed to tuberculous infection, varies in individual cases Sensitivity may exceptionally disappear after only one year or less or it may still be present ten years or more In general one may say that it lasts about five years or more in three-quarters of all intradermally vaccinated children As it is not possible to foretell the duration of tuberculin sensitivity in an individual case, this must be examined by repeated tuberculin tests. If the tuberculin test is negative, the immunity is considered lost, too, and in such individuals the BCG-vaccination is no longer active If the test is positive, the immunity is regarded as present, but will have to be checked again after some time Sooner or later probably all BCG-vaccinated persons who have not been virulently infected lose their tuberculin sensitivity and artificial immunity

A question of practical consequence is, when and how often the tuberculin test should be made? It may happen that the test turns negative six to twelve months after it was last found positive. Theoretically it would be best to control the tuberculin sensitivity at least every year, but this is possible only occasionally. In groups who run a great risk of exposure, for instance, nurses and medical men, annual control is especially indicated, but it is not possible in all vaccinated people. One has to chose the middle path between what is desirable and what is practicable. Exactly where this is is not generally agreed upon.

The problem often solves itself by the facility with which tuberculin testing can be performed. I refer to the groups mentioned earlier: newborns, infants, pre-school children in institutions, children at the beginning and end of school-age; conscripts, women in maternity hospitals, institutionalised and hospitalised persons.

If the examination is performed in the newborn period, the first checking of tuberculin sensitivity may be performed in the first school-year or earlier if the child attends a pre-school institution, the second checking at the end of the school-age, and the third in military service. In the meantime it may be performed occasionally in connection with hospitalisation. As regards special threatened groups of the population the checking ought to be made at shorter intervals. That it is possible to proceed in the way mentioned here is shown by experience in our country, where this schedule is followed.

Tuberculin testing ought to be sufficiently exhaustive to exclude any remaining sensitivity. There is no general agreement about this question; the problem is solved according to personal experience and other influencing factors. Usually a negative Mantoux test of 1 milligram O.T. is considered sufficient to exclude tuberculous infection, and the same strength is often used to exclude remaining tuberculin sensitivity after BCG-vaccination. To use 1 mg. as the first and only test may, however, be dangerous and produce local necrosis of the skin since one can never predict the presence or degree of any remaining allergy. One must start with weaker tests and proceed to stronger ones if the former prove negative. This means that several tests often have to be performed, an inconvenient and time-consuming procedure. For practical purposes a middle course must be followed in this problem also. One has to use as simple and few tests as possible and to disregard the possibility that they are not 100 per cent. reliable. Even if one cannot prove with certainty that all tuberculin sensitivity is lost by this procedure, it is sufficiently reliable to exclude remaining sensitivity that may produce local or systemic inconveniences upon re-vaccination.

The simplest procedures are the ointment or patch-tests, and they are generally used as the first tests. In mass examinations of children they are often the only test employed. In adults with their thicker and less sensitive skin, this method is unreliable. The scarification test (Pirquet test) with concentrated tuberculin and often with added adrenalin is used instead in some quarters. This is followed eventually by a Mantoux test, 0.1-0.5 mg. The latter may be preceded by a weaker Mantoux test, 0 01 or 0 05 mg In our schools and in the military service examinations an ointment or patch-test is used first and if this is negative we continue with 0 5 or 1 mg Mantoux We may proceed from ointment test through Mantoux 0 1 to Mantoux 1 mg

Even with a Mantoux 1 mg negative, a certain degree of tuberculin allergy remains, shown by the type of local reaction after re-vaccination in such cases This slight allergy does not cause any inconvenience It probably is a sign that BCG-immunity is fading and that a booster inoculation is needed If the reasons for the primary vaccination still exist, re-vaccination should be performed and the checking of tuberculin sensitivity made as before

The introduction of BCG-vaccination on a wide scale is admittedly of some inconvenience from a public health point of view it makes the checking of the spread of tuberculous infection and the diagnosis of tuberculous diseases more difficult by the production of artificial tuberculin sensitivity Tuberculosis is, however, not only diagnosed by means of a positive tuberculin test, but also by X-ray of the chest, gastric lavage bacilloscopy, sedimentation test and other less specific clinical signs and symptoms It is the synthesis of these tests that confirms or denies the suspicion of tuberculous disease In one extensive experience in the diagnosis of tuberculous disease in BCG-vaccinated persons, it has only been in exceptionally rare cases that the diagnosis could not be established, and it has never happened that this failure had any unfavourable consequences for the patient The elimination of tuberculin testing as a diagnostic procedure in tuberculous diseases should not therefore be considered so important from a public health point of view as to prevent the introduction of BCG-vaccination

The inconvenience of being unable to check the incidence of tuberculous infection in a BCG-vaccinated population is of greater importance This is, however, mostly in regard to statistics, the changes in the prevalence of tuberculous infection in different age groups and at different periods of years cannot be determined For the public health service, changes in incidence of tuberculous morbidity and mortality are of far greater interest and these two registered subjects can be recorded equally well in a BCG-vaccinated population In such a population the morbidity as well as the mortality of tuberculosis should be and are greatly reduced One has thus to make a choice between increased difficulty in registering the spread of the tuberculous infection and a notable reduction in the registered number of tuberculous diseases and deaths from tuberculosis This choice should not be a difficult one for the public health service (Fig 9)

BCG-vaccination is no panacea which is in itself sufficient to abolish tuberculosis in a community, an opinion which might perhaps have arisen as a result of an exaggerating propaganda BCG-vaccination is only one part in the scheme of the anti-tuberculous campaign Other measures are more important, namely measures aiming at preventing tuberculous infection, at increasing the natural resistance of the population by a satisfactory standard of living, at the early detection of tuberculous disease and giving everyone in need of it adequate treatment When this programme is effective, primary infection is postponed from early childhood to older age groups but at present almost everyone is going to be infected sooner or later The object of BCG-vaccination is to produce artificial specific immunity in those who still are un-infected As we never can tell with certainty when the primary infection may occur and who is going to be infected, the earlier artificial immunity is established the better In a country with high incidence of tuberculosis a general vaccination of children of the youngest age groups is preferable as a public health measure If births generally take place in maternity hospitals the BCG-vaccination is most conveniently performed on newborns without any preliminary tuberculin testing By tuberculin control and revaccination if necessary, the virulent infection, when and if it occurs, is generally prevented from producing clinical primary tuberculosis and early post-primary disease In persons of all age groups running evident risk of exposure, *e g* children in tuberculous homes and hospital personnel, BCG-vaccination should as a public health measure be performed in those still tuberculin negative In addition all other known and available measures of exposure and disposition prophylaxis should be applied at the same time

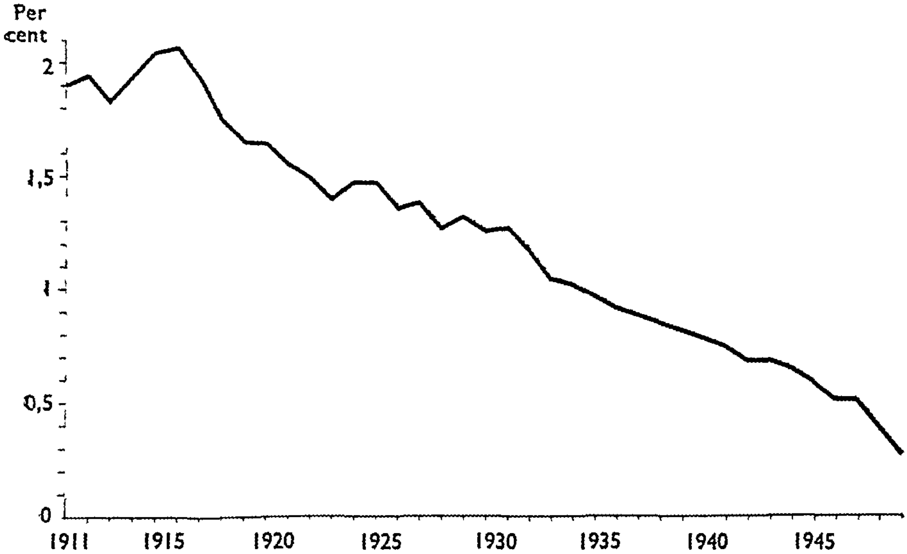

FIG 9—Tuberculosis Mortality Rates in Sweden

THE DETERMINATION OF BACTERIAL SENSITIVITY TO ANTIBIOTICS

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INTRODUCTION

THE need for a simple, expeditious and reliable *in vitro* technique for the determination of the sensitivity of bacteria to antibiotics becomes more essential with the ever-extending use of these drugs

Technical simplicity is essential since requests for these tests are becoming numerically formidable and their value to the clinician depends greatly upon the rapidity with which they can be performed

Realising four years ago that one of the main factors in successful chemotherapy is speed in preliminary bacteriological investigations, one of us (J C G) began to use impregnated filter paper discs implanted on inoculated culture plates as suggested by Morley (1945) and Kolmer (1947) The method is now widely used and many modifications have been developed

The purpose of this paper is to describe the techniques evolved in this department to cover all the antibiotic work required in the hospital We believe the results are adequate for clinical purposes In the preliminary bacteriological reports emphasis is laid upon sensitivity rather than species identification, and with most specimens a statement of the organisms present and their sensitivity, relative resistance, or resistance can be made within twenty-four hours Technical procedures have been simplified and standardised as far as possible so that the results are reliable, easily reproducible, and tedious daily controls are eliminated Moreover, the results are unaffected by minor variations in technique

The use of absorbent paper as a means of carrying penicillin solutions on the surface of solid media for diffusion purposes appears to have been first suggested by Pope in 1940 (Heatley, 1944) A few years later when methods of assaying penicillin were being explored a number of investigators adopted absorbent paper discs in place of formerly used methods (Lamanna and Shapiro, 1943, Foster and Woodruff, 1943, De Beer and Sherwood, 1944, Sherwood, 1944, Epstein, 1944, and Vincent and Vincent, 1944)

Filter paper is the most convenient form of absorbent paper likely to be of uniform quality and for this reason has been used by most workers Uniform quality is most important because the great advantage of paper discs is that each absorbs the same amount of fluid if they are of the same size

As used both in sensitivity determination and in assay, the filter-paper disc method is simply a form of diffusion technique (Sherwood,

1944) As with the other standard diffusion techniques such as the "cup-plate," "ditch-plate" and "cylinder-plate" methods it is affected by certain factors (Vincent and Vincent, 1944, Loo, 1944, Schmidt, 1944, Hobby, 1942) such as the *p*H, the thickness and state of hydration of the medium and by the lag phase of the test organism However, the disc method appears to be less subject to these variable factors than the other methods (De Beer and Sherwood, 1944, Sherwood, 1944, Vincent and Vincent, 1944, Sherwood, 1947) and undoubtedly has definite advantages over them in the ease with which the discs can be prepared and stored, the increase in accuracy due to the amount of fluid which each will absorb, the even and constant contact of the disc with the medium, and the simplicity of the technique which allows replicate tests to be rapidly set up, also the convenience with which the plates can be handled

MATERIALS

Preparation of the Paper Discs—Throughout this work, Whatman No 1 filter paper was used The discs were cut out of sheets of the filter fabric with a paper hole-puncher having a diametral size of 7 mm The discs so produced are fractionally less than 7 mm in diameter and vary insignificantly in size as long as the instrument is sharp and single thicknesses of paper are punched, single sheet punching also ensures that the discs remain discrete and are more easily handled

The discs are counted accurately into lots of 100, and put into 1 oz screw-capped wide-mouthed containers These bottles are then sterilised in the hot-air oven at 150° C for one hour

Preparation of Antibiotic Solutions and Impregnation of the Discs—The solutions are prepared with sterile distilled water and commercial preparations of high standard issued for clinical use One ml of the required solution is then added to each bottle of 100 discs, and as the entire volume is absorbed we may assume that each disc takes up approximately 0 01 ml Thus dilutions of the antibiotics are prepared to contain, in 1 ml, 100 times the quantity required in each disc The amount of each antibiotic per disc is as follows —

TABLE I

Amount of Antibiotic per Disc

Penicillin	Streptomycin	Terramycin	Chloromycetin	Aureomycin
1 unit (0 66 μg)	10 μg	10 μg	25 μg	50 μg

The discs are used wet The bottles may be stored in the refrigerator at 5° C and the antibiotics will retain their potency for at least three months Before use the bottle should be shaken to distribute the discs around the walls of the container and this allows them to be picked up more easily with forceps

The discs are transferred to the inoculated plates with a pair of fine-pointed tweezers The tweezers may be kept with their tips immersed in 70 per cent alcohol which is flamed off before use The tips of the instrument should be flame-sterilised between each transference to prevent contamination, but even without this precaution the contamination rate of the discs is surprisingly low When it does occur organisms of the *Proteus* Group are the common offenders

The Standard Organism —The standard organism used for all the assays and for the preparation of the standard graphs for each antibiotic was a Staphylococcus aureus (S5) This organism has the following sensitivity values as calculated by the recognised procedures —

TABLE II

Minimum Concentration per ml of antibiotic required to inhibit the Standard Staphylococcus

Penicillin	Streptomycin	Chloromycetin	Aureomycin	Terramycin
0 03 units (0 02 μg)	0 5 μg	1 5 μg	0 25 μg	0 25μg

The staphylococcus was grown on nutrient agar and before use was subcultured in nutrient broth at 37° C for eighteen-twenty hours This culture was diluted five times, and the average number of cells per ml was then about 100 million by opacity standards

Preparation of the Standard Graphs —The preparation of the standard graph for penicillin will be described in detail Graphs for the other antibiotics are prepared in a similar manner and do not require description

Solutions of penicillin in distilled water were prepared to give the following range of concentrations per disc —0 001, 0 005, 0 01 0 05, 0 1, 0 2, 0 5, 1 0, 2 0, 5 0 and 10 units The discs were impregnated as previously described Petri dishes containing nutrient agar or blood agar were surface-sown with the standard staphylococcus The nutrient broth culture containing 100 million organisms per ml was flooded on to the surface of the plates with a capillary pipette, the plate tilted and the excess pipetted off The plates were then inverted and dried in the incubator for half an hour at 37° C

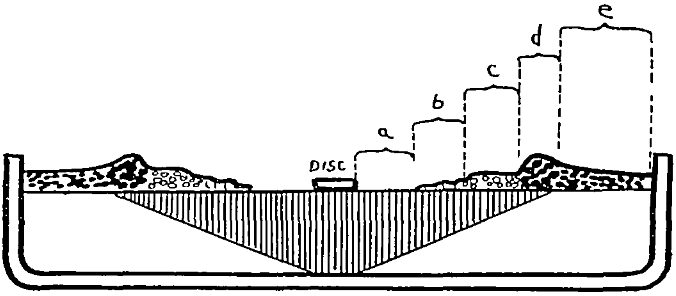
Ten blood agar plates were taken for each concentration of disc, that was, a total of 100 plates, and a minimum of ten estimations for each concentration were carried out The discs may be applied to the centre of the surface or eccentrically, in which case more than one disc can be placed on each plate

Each disc was applied carefully to the surface of the agar without lateral movement once the surface had been touched Where necessary they were flattened down with the points of the forceps

The plates were then incubated for eighteen-twenty hours at 37° C ; the resulting zones of inhibition were measured and plotted on graph-paper

Zones of inhibition —As often described with sensitive organisms, there are several well-defined zones apparent from within outwards around a source of antibiotic on inoculated solid media

They are (Fig 1) (*a*) complete inhibition of growth,
(*b*) delayed growth,
(*c*) lysis, where the shadows of bacterial colonies are present,
(*d*) stimulation of growth, and
(*e*) normal growth



(*a*) Zone of complete inhibition (*b*) Zone of delayed growth
(*c*) Zone of lysis (*d*) Zone of stimulated growth
(*e*) Zone of normal growth

FIG 1 —Petri dish in section showing in diagrammatic form the theoretical concentration gradient of antibiotic after diffusion from the disc Also diagrammatically represented are the various zones of inhibition and growth that may occur

One or more of these zones may not be apparent, depending upon the antibiotic, the sensitivity of the organism and the time of incubation Measurement is best carried out with dividers in a strong reflected light, and we found it most satisfactory to include the zone of lysis, when present, in our measurements The diameter of the zone of inhibition is taken in preference to the radius or the distance from the margin of the disc The results given in Table III are typical of the readings obtained in many experiments

TABLE III

Zones of Inhibition with Different Concentrations of Penicillin per Disc

Concentration of Penicillin per Disc (units)	Zone of Inhibition (m m)
0 001	0
0 005	0
0 01	7 0
0 05	12 8
0 1	19 6
0 2	22 7
0 5	25 5
1 0	30 5
2 0	33 0
5 0	35 1
10 0	38 8

The graph is constructed by plotting the zone of inhibition in mm, against the logarithm of the concentration in microgrammes or units. Over a wide range of concentration the result is a straight line Specimen graphs for penicillin and the other antibiotics are given in Figs 2-6

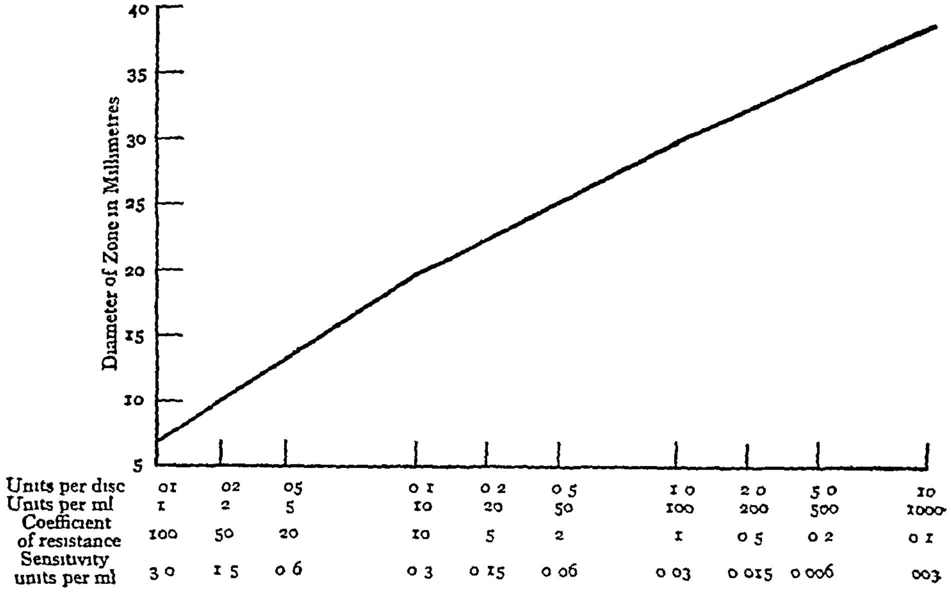


FIG 2—Standard Graph for Penicillin

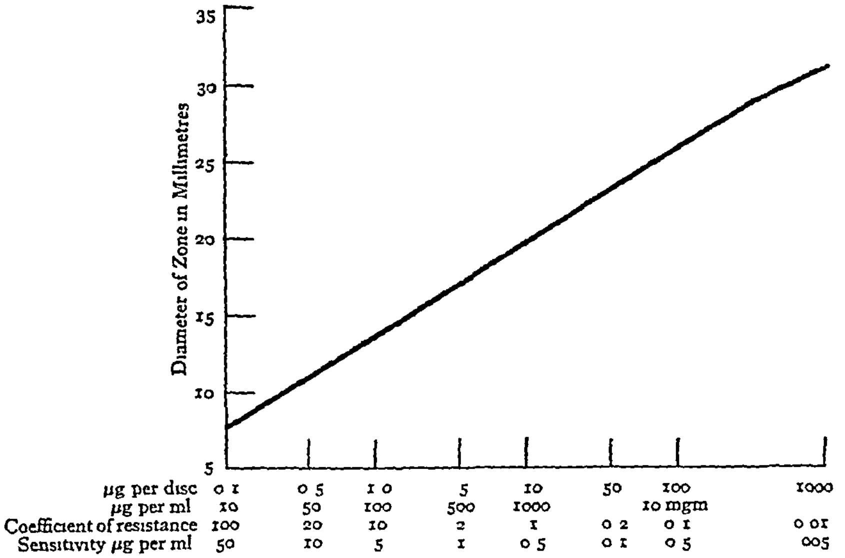


FIG 3—Standard Graph for Streptomycin

It should be noted that the smallest zone of inhibition that can be measured is that which is just visibly greater than the disc, about 7 0 mm in diameter

As can be visualised from Fig 1 the concentration of the antibiotic constantly decreases with distance from the disc Some antibiotics

Note—Those wishing to follow the detailed technique described in Figs 1 to 6 should transcribe and enlarge the graphs on sectional paper diffuse more rapidly than others If the organism is inoculated before applying the disc to the medium, diffusion must take place rapidly enough to produce clear-cut zones of inhibition If conditions are identical in repeated tests, the rate and extent of diffusion will remain constant, and identical zones of inhibition will be obtained

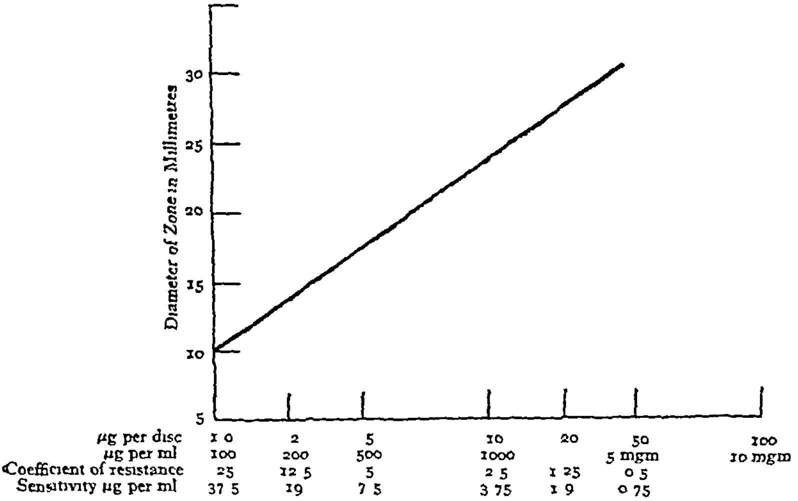


FIG 4—Standard Graph for Chloromycetin

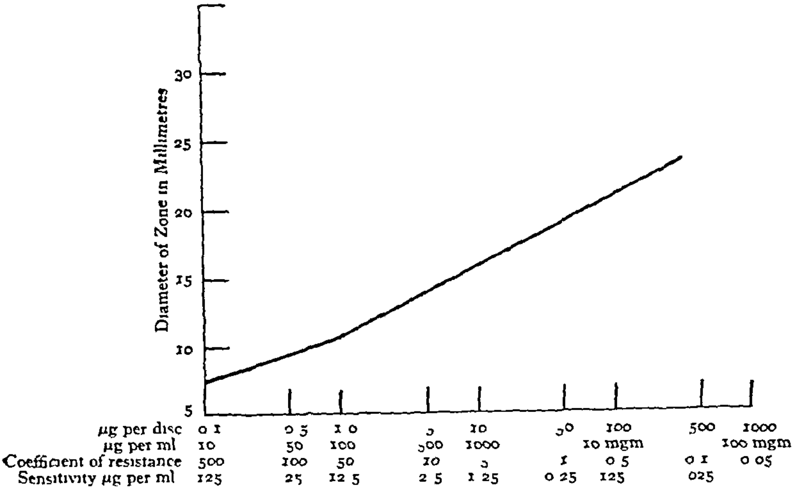


FIG 5—Standard Graph for Aureomycin

Absolutely constant conditions are impractical in routine work, we have investigated the variable factors to determine their effect on the results and to decide upon the latitude which may be allowed without significant alteration in the zones of inhibition As a result of these experiments we have been able to adopt certain standards and procedures which constitute our modifications of the original method

EXPERIMENT 1 *Variation in the Size of Disc*—Different sizes of disc were prepared of diameter ranging from 4 to 12 mm Using 1 0 ml of fluid the larger discs are not uniformly saturated as 100 will absorb more than this amount The smaller discs are uniformly saturated but do not absorb all the fluid The results obtained over a number of experiments with discs of different sizes is shown in Table IV The size of disc, 100 of which will absorb 1 0 ml of fluid, is about 7 0 mm. The disc of 6 8 mm , being slightly smaller, ensures that each disc is fully saturated when 100 are mixed with 1 0 ml of solution and the reduction of antibiotic content is insignificant For this reason the 6 8 mm disc was adopted as our standard

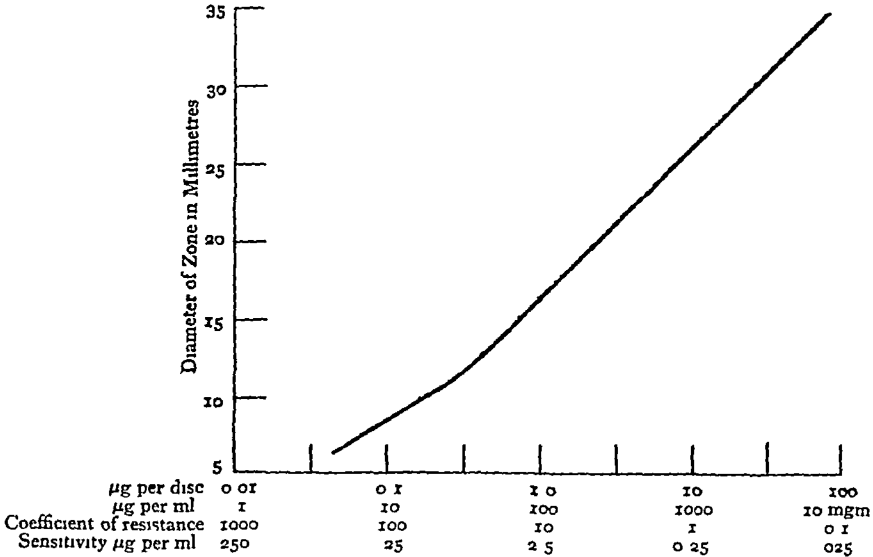


FIG 6—Standard Graph for Terramycin

EXPERIMENT 2 *Variation in Type of Paper*—6 8 mm discs of Whatman No 1, No 2 and No 40 and of thick and thin blotting paper were used under conditions similar to those in Experiment 1 There was little variation between the zones obtained with the filter papers but the blotting paper gave unsatisfactory results since a disc of this size absorbs more than 0 01 ml The results then depend upon the amount of fluid that the paper is capable of absorbing

TABLE IV

Zones of Inhibition with Different Sizes of Disc

Size of Disc	Number of Tests	100 Discs to 1 0 ml Solution (zones in mm)	Discs Individually Saturated (zones in mm)
12 0	50	35	34
8 0	50	33	32
6 8	50	30	30
5 0	50	27	27

EXPERIMENT 3 *Conditions of Storage*—Discs prepared in the way already described were stored under different conditions and then tested for potency as shown by the zones of inhibition As can be seen from Table V the discs retained their potency for a longer period in the

refrigerator than at room temperature, and longer when wet than when dry. The variation in zone diameter was also less when wet than when dry.

Discs saturated with aqueous solutions of the other antibiotics were stored in the wet state and tested for potency after lengthening periods of time. The results are given in Table VI.

TABLE V

The Effect of Storage and Time on Potency of Discs

Penicillin 1 Unit Discs		*Time* (Zones of inhibition in mm.)				
		1 Week	4 Weeks	2 Months	3 Months	4 Months
Wet	Room temperature	30	29	29	28	28
	4° C.	30	30	30	30	29
Dry	Room temperature	29	29	28	27	26
	4° C.	29	28	27	27	27

TABLE VI

Showing the Effect of Time on the Potency of Discs

Antibiotic µg./Disc	Time in Months (Zones of inhibition in mm.)									
	1	2	3	4	5	6	9	12	18	24
Streptomycin 10	18	18	18	18	18	18	17	17	16	15
Chloromycetin 25	30	30	30	30	30	30	27	25		
Aureomycin 50	21	21	20	20	20	18				
Terramycin 10	27	26	23	23						

TABLE VII

Effect of the Amount Inoculum on Zone of Inhibition

Inoculum (orgs./ml.)	Penicillin Discs Containing 1.0 Units		
	Number of Tests	Zone of Inhibition in mm.	Remarks
50,000	50	37.5	Individual colonies on plate
500,000	50	30.5	Almost confluent growth
5,000,000	50	30.5	Confluent growth
50,000,000	50	30.0	Confluent growth
100,000,000	50	30.5	Confluent growth
200,000,000	25	30.0	Confluent growth
500,000,000	25	29.0	Confluent growth
1,000,000,000	10	28.5	Confluent growth

EXPERIMENT 4. *Amount of the Inoculum.*—In the standard procedure already described the culture plates are seeded with broth containing approximately 100 million staphylococcal cells per mm. The effect of varying this inoculum was tried and as will be seen from Table VII, within fairly broad limits, there is no great variation in the zones of inhibition produced by discs of the same potency.

That this does not hold true for all antibiotics, particularly Terramycin, is shown in Table VIII where the effect of a ten-fold variation in inoculum is shown for each agent

EXPERIMENT 5 *Age of the Inoculum* —The older the culture, the smaller the number of viable cells it will contain, the lag period for these cells will be longer than for those used in the logarithmic period of growth, as in experiment 4 However, in practice the age of the cells of the inoculum has an insignificant effect on the zone diameter

TABLE VIII

The Effect of Inoculum on Zones of Inhibition

Antibiotic	Inoculum (cells/ml)	Zone of Inhibition (mm)
Streptomycin	20,000,000 200,000,000	18 17
Chloromycetin	20,000,000 200,000,000	30 28
Aureomycin	20,000,000 200,000,000	21 18
Terramycin	20,000,000 200,000,000	27 21

EXPERIMENT 6 *Variation in the Method of Inoculation* —Pour plates of nutrient agar previously seeded with the staphylococcus are not recommended because the zones of inhibition are more difficult to read and their preparation is more complicated Surface seeding gives the best results when the distribution of the organisms is reasonably uniform A small amount of broth culture may be spread over the surface of the medium with a suitable instrument and allowed to dry, if carefully done this results in a uniform growth However it is easier to pour an excess of the diluted broth over the surface of the medium, drain off the excess, and dry in the incubator

TABLE IX

Showing Effect of Different Methods of Inoculation Plates

Method of Inoculation	Inoculum (orgs /ml)	Zone of Inhibition (mm)
Pour plates	100,000,000	28
Fixed volume of inoculum	100,000,000	30
Flooded plate	100,000,000	30

The zones of inhibition obtained by these methods are similar (Table IX)

The time of drying the plates in the incubator at 37° C does not affect the zones of inhibition provided that it does not exceed two hours After two hours the plates become dehydrated to some extent and colony growth begins , both factors influence test readings

EXPERIMENT 7 *Type of Medium Used*—The pH of the medium has been shown to have a marked effect on the zones of inhibition of growth of penicillin (Schmidt, 1944), streptomycin (Loo, 1944) and aureomycin (Pratt and Dufrenoy, 1948, and Ingram, 1950) We did not pursue this as, with few exceptions, the routine laboratory media have a pH around 7 2-7 6 Variation within these limits has insignificant effect upon the zones obtained with any of the antibiotics

The agar base of the medium must be homogeneous , otherwise there will be irregularities in diffusion

The effect of the concentration of agar, and the addition of other materials such as blood (blood agar medium) and bile-salts (McConkey's medium) were investigated The more concentrated agar (Table X) retards diffusion of penicillin since the zones of inhibition are smaller but there is no significant difference within the range of concentrations usually used in preparing laboratory media (1 5-3 0 per cent) The zones of inhibition obtained on blood agar medium and on McConkey's medium are the same as those obtained on nutrient agar medium

TABLE X

Showing the Effect of Concentration of Agar and of Other Ingredients in the Medium

Concentration of Agar	Medium	Zones of Inhibition in mm				
		Penicillin	Strepto mycin	Chloro mycetin	Arueomycin	Terramycin
1 per cent.	Nutrient agar	29	18	30	20	26
2 ,,	,,	30	19	29	20	25
3 ,,	,,	30	19	29	18	25
4 ,,	,,	29	18	29	18	25
6 ,,	,,	23	16	25	16	24
2 ,,	Blood agar	30	19	30	19	24
2 ,,	McConkey	30	20	30	19	24

EXPERIMENT 8 *Thickness of the Medium* —Other conditions being equal, it is the depth of the medium which determines the extent of diffusion of the antibiotic (De Beer and Sherwood, 1944) , the thicker the agar medium the smaller the zone of inhibition When the medium is very thin there is the additional factor of indistinct margins to the zones of inhibition, making exact measurement difficult Using the plates poured daily for routine use in the laboratory, we found no significant variation on this account

We use 7 cm Petri dishes for routine work and find 5 ml of medium satisfactory Table XI shows the zones of inhibition obtained with thicker and thinner layers of medium

EXPERIMENT 9 *Time of Incubation*—Penicillin and the other antibiotics diffuse rapidly outwards before any appreciable growth has taken place We may thus disregard the effect of time on the diffusion of the active substance

The standard organism grows appreciably in six-eight hours' time, and by then there are well-marked zones of inhibition of growth with penicillin These are zones of absolute inhibition and correspond in size to the zone of absolute inhibition seen after twenty hours The zone of lysis forms between ten-twenty hours and is included by us in the zone measured However, there is no reason why the zone of absolute inhibition should not be used as the criterion and read at eight hours if desired , this is usually inconvenient unless the plates are inoculated first thing in the morning Further, it will not be feasible in the sensitivity determination of a slow-growing organism The zone of lysis does extend after twenty hours and is appreciably larger at forty-eight hours , for this reason readings should not be too long delayed

TABLE XI

Showing the Effect of the Thickness of the Medium

Size of Plate Diameter in cm	Amount of Medium per Plate	Thickness of Medium	Zones in mm				
			Penicillin	Strepto mycin	Chloro mycetin	Aureomycin	Terramycin
7	3 0 ml	0 8 mm	33				
7	5 0 ,,	1 3 ,,	30	20	29	18	27
7	7 5 ,,	2 0 ,,	28				
7	10 0 ,,	2 6 ,,	26	20	27	17	25
7	15 0 ,,	4 0 ,,	22				

EXPERIMENT 10 *Incubator Temperature*—Variation within the usual range of incubator temperatures used in the laboratory produces little effect upon the zone of inhibition provided that growth actually takes place

SUMMARY OF EXPERIMENTS 1-10

As a result of these experiments the following points are of importance in obtaining consistent results

Petri-dishes containing a uniform thickness of medium are used They are surface-sown with an over-night broth culture of the standard organism for assay purposes, or with the test organism, for sensitivity determination The plates are then dried for thirty minutes at 37° C , the discs are then applied It is essential that the discs be of uniform size and material, and similar to those used in the preparation of the standard graphs Measurements are made after eighteen-twenty hours' incubation

Adequate results can be obtained with routine laboratory plates sown in a variety of ways , these are described below

EXPERIMENT 11 *Test of the Reproducibility of Results*—1000 penicillin 1 unit discs were taken from freshly prepared stock and used under the conditions just described Table XII gives the results

THE DETERMINATION OF THE SENSITIVITY OF AN ORGANISM

The exact identity of the organisms present is unnecessary for sensitivity determinations as long as the colonies are individually recognisable on the medium

An initial sensitivity result can be obtained from the primary cultures by placing discs on suitably inoculated plates at the time of inoculation. The variety of media inoculated, and atmospheres of incubation, must be sufficiently wide to ensure growth of any species of micro-organism likely to be present For example, discs must be placed on anærobic blood medium if anærobic streptococci are anticipated This test may be regarded as a screening test

The Screen Test—This may be varied to suit different conditions.

TABLE XII

Results of 1000 *Consecutive Tests with* 1 *Unit Penicillin Discs*

Number of Tests	Mean of Zones mm	Standard Deviation	Standard Error of Mean
1000	30 13	1 075	0 034

(1) Where the sensitivity to one antibiotic only is required (*a*) Area of initial inoculation in primary cultures of the specimen is made larger than usual so that it covers about one-third of a 3½ ins Petri-dish and is spread as uniformly as possible The disc containing the antibiotic is applied to the centre of the area After incubation the zone of inhibition of growth is measured and in most cases will give a satisfactory assessment when compared with the more detailed test carried out at a later stage

There will be a number of tests where the result cannot be assessed properly as (i) where more than one species are present, the growth of an insensitive organism occasionally masks the sensitivity of a sensitive organism, and (ii) where the inoculum is so sparse that a satisfactory zone of inhibition is not formed (*b*) Alternatively, a plate may be inoculated especially for the discs by stroking out the material with a loop or swab across the whole area of the plate as uniformly as possible

(2) Where the sensitivity to more than one antibiotic is required

A large Petri-dish or several smaller dishes should be inoculated as described in (1) (*b*) and the individual discs applied at suitably spaced intervals A 4 in Petri-dish will accommodate five discs comfortably

Method of Reading Results—The diameter of the zone produced by the disc on the plate cultures of the organism is measured in mm.

From the standard graph prepared for the particular antibiotic, the concentration of the antibiotic to which the organism is sensitive, can be read off directly in figures together with its coefficient-of-resistance compared with the standard Oxford Staphylococcus

The initial screening test will give information usually adequate for clinical purposes and no further sensitivity determination will be necessary However, it is often desirable to carry out further tests in order to obtain a more exact estimation or to determine the sensitivity to additional antibiotic substances In such cases we carry out the sensitivity determination on subcultures of the test organism with a standardised inoculum

The Sensitivity Test on Subcultures of the Test Organism —This can be carried out as soon as the organisms have been isolated Subcultures are made in a suitable fluid medium and are usually incubated for eighteen hours, but often for less The resulting cultures are diluted to give approximately 100 million cells per ml by opacity standards, and the test plates are surface seeded One plate is sufficient for each organism to be tested, but as many as desired may be inoculated as duplicates The disc for each antibiotic is then applied and the zones of inhibition growth read after eighteen-twenty hours' incubation

The sensitivity may be read off from the standard curve as before

In a case where the result of a sensitivity test is urgently required and it has not been feasible to carry out the screening test, for example with a blood culture, a heated blood agar plate may be seeded with material from the primary culture in the usual way and the required disc applied After six-ten hours the zone can be measured if the organism has grown sufficiently This zone will differ from the zone that would be obtained after eighteen-twenty hours, and due allowance must be made in interpreting the sensitivity values

THE REPORTING OF RESULTS

Only in special cases such as septicæmia and in research work is it necessary to know the exact level of sensitivity expressed in microgrammes per ml , units or coefficient of resistance An opinion expressed in terms such as " sensitive," " relatively resistant " and " resistant," should suffice for clinical purposes

Since *in vivo* sensitivities cannot be accurately gauged from *in vitro* levels of sensitivity, mathematical expressions of these might even be misleading We therefore use descriptive words, but relate them to two arbitrary ranges of *in vitro* concentrations , one range (Table XIV) is used in reporting examinations of the urine, and the second (Table XIII) is used for all other specimens , it is based on the average systemic levels of the antibiotics usually obtained during treatment

In determining these ranges we have attempted to combine the experience of our clinical colleagues in Edinburgh with our reviews of follow-up bacteriological examinations

THE PRESENCE AND DETECTION OF RESISTANT COLONIES

Occasionally within the clear zone of inhibition, a few colonies may grow more or less right up to the disc. If these colonies are of the same species then they may be regarded as resistant variants. Alternatively they may be another species separated by the selective activity of the antibiotic.

The resistant colonies may be subcultured and the actual sensitivity determined. Their presence will usually weigh heavily against the use of that particular antibiotic.

TABLE XIII

Correlation of Clinical Terms with Sensitivity Values for Usual Systemic Concentrations

Term for Clinical Use		Antibiotic *In vitro* Levels in µg/ml				
		Penicillin	Streptomycin	Chloromycetin	Aureomycin	Terramycin
SENSITIVE	Up to	0.3	1.0	2.5	2.5	1.0
RELATIVELY RESISTANT	Up to	1.0	10.0	10.0	10.0	5.0
RESISTANT	Greater than	1.0	10.0	10.0	10.0	5.0

TABLE XIV

Correlation of Clinical Terms with the Sensitivity Values for Usual Urinary Concentrations

Term for Clinical Use		Antibiotic *In vitro* Levels in µg/ml				
		Penicillin	Streptomycin	Chloromycetin	Aureomycin	Terramycin
SENSITIVE	Up to	50	10	10	15	10
RELATIVELY RESISTANT	Up to	100	100	40	100	25
RESISTANT	Greater than	200	100	40	100	25

A heavy inoculum of 1000 million organisms, or more per ml may be used to seed the test plates where it is desired to determine the presence or absence of resistant variants in a culture. This is especially applicable to urinary tract pathogens. The heavier the inoculum, the greater the chance of isolating resistant variants. The practical use of this has already been shown in the case of Myco. tuberculosis by Tinne (1950).

PROCEDURE WITH ANTIBIOTICS OTHER THAN PENICILLIN

As we already said the procedure given is the same for antibiotics in common use at present Streptomycin and chloromycetin behave exactly like penicillin with regard to these tests, further discussion may therefore be confined to aureomycin and terramycin

(1) *Aureomycin* —This antibiotic is susceptible to certain substances present in blood, and sometimes in peptones, used to make media (Herrell, 1950, Bliss and Chandler, 1948) so that it tends to be inactivated during the period of growth of the test organism This is one of the chief reasons for the relatively small zones of inhibition with aureomycin and the tendency for the test organism to grow inwards towards the disc during the later hours of incubation We can overcome this is three ways

(*a*) By using medium with a *p*H of 5 5 (buffered) when the inactivating substances are rendered inert and the zones of inhibition are much larger and better defined Unfortunately many bacteria to be tested will not grow at this *p*H level and also we must admit that conditions will be even further removed from those likely to be present *in vivo*

(*b*) By adopting the policy, already referred to, of reading the zones of inhibition after eight hours' incubation

(*c*) By incorporating reducing substances in the medium or incubating under anærobic conditions (Price, Randall and Welsh, 1948)

(2) *Terramycin* —The zones of inhibition around a terramycin disc are clear cut in the early hours of incubation and we have adopted the technique of reading results after eight-ten hours' incubation

There is a great difference between the bacteriostatic and bactericidal concentrations of terramycin for most organisms, this would appear to be the reason for the diminished zone of inhibition during the later hours of incubation This of course means that in accepting the eight-hour zones we are taking the " bacteriostatic " level, the " bactericidal " level is related to the usually much smaller zone obtained after longer incubation This reasoning is substantiated by parallel serial dilution tube tests where the wide gap between bacteriostatic and bactericidal levels is obvious

THE DETERMINATION OF THE SENSITIVITY TO STREPTOMYCIN OF MYCO TUBERCULOSIS

The determination of the sensitivity of *M tuberculosis* to antibiotics presents difficulties—among others, the particularly slow rate of growth of the organism in culture

We have found that it is possible to use the disc diffusion technique for the sensitivity determination of this organism to streptomycin So far we have carried out only a limited number of tests and are attempting to improve the technique, we mention this merely to indicate that satisfactory zones of inhibition can be obtained

Lowenstein-Jensen, or similar medium, is coagulated in Petri-dishes so that the thickness of the medium is similar to that used for the routine sensitivity tests Material containing the tubercle bacillus (this may be a concentrate of sputum, etc , known to contain the bacillus, or an emulsion of a culture of the organism) is spread over the surface of the medium as uniformly as possible, and allowed to dry The discs of streptomycin (10 μg /disc) and Para-amino salicylic (200 μg /disc) are then applied to the surface of the medium The space between the lid and the base of the Petri-dish is sealed with vaseline-paraffin wax mixture to prevent dessication, and the plates are incubated for the time required to produce visible growth Aeration of the cultures is carried out at the usual intervals

Using the standard H 37 Rv strain of M tuberculosis (kindly supplied by Professor C P Beattie) the zones of inhibition obtained with the streptomycin disc correspond fairly well with the calculated zone for an organism sensitive to 0 5 μg /ml of streptomycin

Satisfactory zones are frequently obtained within ten days, and as this is possible with primary cultures of sputa, the method may have some practical application

THE OBSERVATION OF THE PRESENCE OR ABSENCE OF SYNERGISTIC INHIBITORY EFFECT BY COMBINATIONS OF ANTIBIOTICS

The combination of two or more antibiotics is being more widely used in treatment with or without definite evidence that the pathogens are more sensitive to the combination than to one or other of the components of the mixture, alone The effect of such a combination on bacteria can be shown when antibiotics are mixed in fluid media but has been more difficult to demonstrate with solid media using diffusion techniques Placing a disc of antibiotic A on top of a disc of antibiotic B, or *vice versa* may not be very satisfactory as A may diffuse more rapidly and to a greater extent than B, so that all the inhibitory effect is due to A, B being present in effective concentration only within the zone of inhibition due to A

To forecast the synergistic effect of combinations of antibiotics we use the disc-diffusion method after the manner of Lamanna and Shapiro (1943) The sensitivity of the test organism to antibiotics A and B of the intended combination is determined in the usual way Next, a fresh culture plate is sown with the test organism, and discs of A and B are applied at a distance " X " mm apart, where X equals $a+b$, a being the radius of the zone of inhibition to antibiotic A, and b the radius of the zone to B After incubation the two zones of inhibition will just make contact and there will be a thin wedge of growth on either side of the point of contact of the zones When there is appreciable additive or synergistic inhibitory effect (Kolmer, 1945) of individually sub-inhibitory concentrations of antibiotics A and B, the growth in the area of the wedges will be inhibited and can be seen without difficulty

So far we have not attempted to interpret this in a quantitative manner

Mutual interference of antibiotics may also be demonstrated by this method

COMPARISON OF THE DISC DIFFUSION METHOD WITH OTHER DIFFUSION METHODS AND THE SERIAL DILUTION TUBE METHOD

The "ditch" (Fleming, 1929) and "cylinder" (Foster and Woodruff, 1943, Abraham, 1941, Foster and Woodruff, 1944) plate techniques give results comparable with the disc modification but they are infinitely more tedious, less accurate and give less easily reproducible results

The serial dilution tube method is very much more laborious than the disc-diffusion method In routine work mistakes tend to occur more easily with this method, pipetting errors being especially common The medium must adequately support the growth of the test organism otherwise very discrepant results may be obtained When the disc-diffusion method was carried out in parallel with the serial dilution tube method, closely similar results were obtained

In one experiment, 100 consecutive cases of staphylococcal infection were taken and the sensitivity of the infecting organism determined by the screen test we have described for primary cultures, after subculture the sensitivity was again determined, both by the serial dilution tube method and by the diffusion method There was satisfactory correlation between the results of the screen test and those of the serial dilution tube test, and even closer agreement between the tests on subculture 95 of the 100 cases gave sensitivity results which agreed in all three tests Of the remaining 5 cases, 3 gave results in the screen test which placed them in the "relatively resistant" zone of the penicillin graph, on subculture they proved to be fully resistant to 20 units by both the serial dilution tube method and by the disc method A fourth organism was "sensitive" by the screen test, and sensitive to 1 0 unit/ml by the tests on subculture In the fifth case the organism, sensitive to 0 2 units by the screen test and diffusion test on subculture, was found to be resistant to 20 units by the serial dilution tube method

This experiment is typical of our experience and shows that the diffusion technique is as accurate as the more complicated tube test for all purposes In addition it has the advantage of simplicity, speed and easy reproductibility

THE ASSAY OF ANTIBIOTIC SUBSTANCES

The number of requests to assay antibiotics in body fluids is small in a routing hospital laboratory

Paper discs may be used to assay these substances and, within the limitations of the method, provides a very simple and rapid procedure The chief limitation is in the amount of antibiotic that can be detected

This corresponds to the smallest amount which will give an appreciable zone of inhibition around the disc , as the disc will only absorb 0 01 ml , the amount of antibiotic present in 1 0 ml of the test fluid must be considerable The practical lower limits assayable for each antibiotic with the standard staphylococcus are as follows —

TABLE XV

Assayable Lower Limits ug /ml

Penicillin	Streptomycin	Chloromycetin	Aureomycin	Terramycin
2 0	15 0	75 0	10 0	10 0

The sensitivity of the test may be increased by layering discs, one on top of the other, up to a maximum of 4, and this has been found to give fairly satisfactory results In this manner concentrations of penicillin of 0 5 units per ml may be assayed

The range of the test may also be increased by using a particularly sensitive organism for each antibiotic This necessitates the construction of separate standard curves, and will not be considered here

In our opinion the disc method is of value in assaying specimens of urine and other fluids where the concentration expected is high , it is also useful for checking assays on laboratory standard solutions of antibiotics

The Method of Assay —The technique is the same as that described for determinations of the sensitivity of an organism except that the unknown quantity is the amount of antibiotic in the disc

The standard staphylococcus in eighteen-hour broth culture, 100 million cells per ml , is surface seeded on nutrient agar plates which are then dried for thirty minutes One ml of the fluid for assay may be added to 100 sterile discs in a bottle, or alternatively, individual discs may be soaked with the fluid by dipping The latter method is not quite so accurate but is more economical in discs Care must be taken not to carry over an excess of fluid, and this is best avoided by draining the disc against the side of the container

The zones are read after eighteen-twenty hours , the concentration per disc or ml can be read off from the standard curve for the particular antibiotic concerned

DISCUSSION

Clinical diagnosis is not a dependable guide to the microbial flora present and certainly not to their antibiotic sensitivity Bacteriological data not only serve as guides to the drug of choice, and alternatives, but also as an indication of the adequate dose

Clinicians agree in principle that in most bacterial infections the sensitivity of the causative organism should be determined before chemotherapy is begun, but inadequate laboratory resources, inconveniently situated laboratories or delay in the receipt of laboratory advice make this difficult or often impossible Since progress has been made in the development of rapid laboratory techniques for the purpose, and the range of available antibiotics is still expanding—each with its own antimicrobial "spectrum"—it can be categorically stated that specimens should now be taken for bacteriological examination before these remedies are exhibited and that it is advisable to know the pre-treatment sensitivity of the causative organism Of course this may be impossible if no material containing the causative organism is available, or if, as in an emergency, it is necessary to give an antibiotic before the result of laboratory data is to hand

The premature use of antibiotics for the alleviation of symptoms, *e g* pain or fever, or as an aid to diagnosis is to be deprecated This practice masks symptoms, delays effective treatment, and complicates laboratory identification of the causative organism, the bacteria assume bizarre characters and growth may be temporarily reduced

A working knowledge of the anti-microbial "spectrum" possessed by each of the five antibiotics in general use, is of advantage, but this has been perhaps over emphasised by those concerned in the production and distribution of these drugs It should be remembered that all organisms of a particular group or species are alike in their sensitivity to one particular antibiotic, to give only a few examples, the antibiotic of choice for coagulase-positive staphylococci, streptococci other than those of Lancefield's Group A, and Gram-negative bacilli of wounds and of the urinary tract, can only be determined by a sensitivity test in each individual case

In practice there is no reliable guide to the therapeutic use of antibiotics other than *in vitro* sensitivity allied to clinical experience There are individual cases in which the taking of a pre-treatment specimen for bacteriological examination is inexpedient there are others such as meningococcal meningitis in which the exhibition of a sulphonamide should not be delayed for sensitivity determination but in general the choice and dose of antibiotic should be guided by the bacteriological findings in each individual case

The object of the work presented in this paper has been the adaptation of tests in connection with antibiotics to routine bacteriological procedures in a hospital laboratory

When the laboratory and clinical points of view are correlated there is no doubt that diffusion methods with solid media are the methods of choice, they show more clearly than other test methods the different ways in which an organism may react to antibiotics *in vitro*

Of the diffusion methods, the impregnated disc technique is the most simple and flexible We have adapted the technique to cover all antibiotic work likely to be required of a hospital laboratory and we have found the results adequate for practical purposes

In most laboratories the staff engaged in preparing and setting primary cultures could undertake the screen test on every spec sent for bacteriological examination—without excessive increase in the amount of work when the tests become routine Subculture sensitivity tests are a different matter, but one worker can undertake more than 100 in a day if necessary, and the difference in time required to apply the separate discs for each additional antibiotic is small compared with the time taken in preparing and seeding the plates

It is suggested that sensitivity levels be reported in the form of descriptive words correlated with levels known to exist in body fluids when the patient is under treatment Owing to the higher levels of various antibiotics in the urine as compared with the concentration obtainable in the blood and tissue fluids, we use two scales for the interpretation of *in vitro* levels

It is as well to remember that we are as yet at an elementary stage in correlating the clinical administration of antibiotics with *in vitro* sensitivity determinations designed to give some idea of the amount of antibiotic required

It is possible that the sensitivity determination, using the primary culture, gives a result which is actually more nearly related to *in vivo* conditions, especially when multiple species of organisms are concerned The mutual effect of the organisms on one another is coupled with the action of the antibiotic, so the test result may well differ from that obtained when the organisms are tested in pure subcultures

If the discs are applied to primary culture plates, apparent anomalies may occasionally influence the reading of the result, the inhibition by a given antibiotic may differ under ærobic and anærobic conditions It may be that the organism *in vivo* is subject to a reduced oxidation-reduction potential, in such a case the anærobic sensitivity level would perhaps have greater significance As it is not possible to decide the actual conditions in the patient, it is our custom to report the lower level of sensitivity, where there is any clinical reason for so doing

We believe that the study of the zone of inhibition surrounding the source of an antibiotic on a Petri-dish, can give a great deal of information about the action of the antibiotic on the organism under test, and that this information may be applicable to clinical work The appearance of a few resistant colonies within the zone of inhibition of the majority is of significance The merging of zones between two antibiotics is an indication of additive or synergistic inhibition The difference between the bactericidal and bacteriostatic effects of an antibiotic can be very clearly seen and would appear to have great significance with agents such as terramycin Using the serial dilution tube technique, visual end-points give sensitivity values which are lower than the bactericidal level determined by the recovery of viable cells from the apparently clear tubes This can be seen on diffusion plates where the well-marked zone of inhibition, present during the early hours of incubation, is encroached upon during the later hours Within the bactericidal concentration for the test organism, all cells on the surface of the medium are killed and at no time will there be growth in the zone, no matter how long the plate is incubated This zone of complete inhibition corresponds to the bactericidal level Outside the zone of complete inhibition the concentration falls to the bacteriostatic level and within the zone, corresponding to this second concentration, the cells on the surface of the medium are not killed; the lag period of growth is increased Once this lag period is over, growth is demonstrated by a fine haze over the surface of the medium spreading inwards to the periphery of the zone of complete inhibition With terramycin this zone of delayed growth or bacteriostasis, is particularly large, varying of course with the particular organism concerned Probably this has a distinct significance with regard to the outcome of treatment with this drug

SUMMARY

Details are given whereby the disc method may be incorporated in the procedures of any hospital laboratory for all antibiotic work

The methods described include a screening sensitivity test on primary plate cultures, a sensitivity test on subcultures, a method by which antibiotic synergism against any particular organism may be observed, and lastly, a method for the assay of antibiotics in fluid

The few simple materials required are available in any hospital laboratory and no special culture media are necessary No tedious controls are involved and dilutions of antibiotics need be made only once in three months

As a screening test the method may be allied with the usual procedures involved in the isolation and identification of micro-organisms in hospital laboratories , the few additional manipulations are extremely simple and may be performed within a few seconds The incorporation of the technique in routine bacteriological examinations actually facilitates the isolation of micro-organisms present in many specimens , the organisms and their sensitivity to the various antibiotics can generally be reported from primary cultures—that is to say, within twenty-four hours of the time the specimen is received

By merely measuring the diameter of the zone of inhibition the sensitivity level and coefficient of resistance, compared with the standard staphylococcus, may be obtained from standard graphs These are included in the text for terramycin, penicillin, streptomycin, chloromycetin and aureomycin , assays may be performed with equal facility

Experiments performed to test accuracy show that this is adequate for clinical purposes In other respects it has practical advantages over other techniques

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REFERENCES

ABRAHAM, E G *et al* (1941), *Lancet*, 2 177
DE BEER, E J, and SHERWOOD M B (1944) *Journ Bact* 50 459
BLISS, E A, and CHANDLER C A (1948), *Proc Soc Exp Biol Med*, 69, 467

EPSTEIN, J A *et al* (1944), *Journ Lab Clin Med*, 29, 319
FLEMING, A (1929), *Brit Journ Exp Path*, 10, 226
FOSTER, J W, and WOODRUFF, H B (1943), *Journ Bact*, 46, 187
FOSTER, J W, and WOODRUFF, H B (1944), *Journ Bact*, 47, 43
GARROD, L P (1950), *Brit Med Journ*, 2, 617
HEATLEY, N G (1944), *Biochem Journ*, 38, 61
HERREL, W F (1950), *Amer Journ Med Sci*, 249, 570
HOBBY, G L *et al* (1942), *Proc Soc Exp Biol Med*, 50, 277
INGRAM, G I C (1951), *Journ Gen Microbiol*, 5, 22
KOLMER, J A (1947), *South Med Journ*, 40, 72
KOLMER, J A (1945), *Amer Journ Med Sci*, 215, 136
LAMANNA, C, and SHAPIRO, I M (1943), *Journ Bact*, 45, 385
LOO, Y H *et al* (1944), *Journ Bact*, 50, 701
MORLEY, D C (1945), *Journ Path Bact*, 57, 379
PRATT, R, and DUFRENOY, J (1948), *Journ Bact*, 55, 727
PRICE, RANDALL, and WELCH (1948), *Ann New York Acad Sci*, 51, 211
SCHMIDT, W H, and MOYER, A J (1944), *Journ Bact*, 47, 199
SHERWOOD, M B (1944), *Science*, 99, 247
SHERWOOD, M B (1947), *Science*, 105, 414
TINNE, J E, and HENDERSON, J L (1950), *Lancet*, 2, 901
THOMSON, B A (1950), *Journ Clin Path*, 3, 118
VINCENT, J G, and VINCENT, H W (1944), *Proc Soc Exp Biol Med*, 55, 162

STAPH AUREUS AIR INFECTION IN A MATERNITY HOSPITAL

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NEWBORN infants are especially susceptible to infection by *Staph. aureus* Even the well-run maternity hospital often has a high incidence of infection among the babies during their week or so of residence. Pemphigus neonatorum, minor septic skin lesions, umbilical sepsis, nasal infection, blepharitis and conjunctivitis are common, and some cases occur of staphylococcal pneumonia, meningitis and osteomyelitis (Cass, 1940, Ludlam, 1947)

Investigations such as those of Elliot, Gilliespie and Holland (1941), Duncan and Walker (1942) and Allison and Hobbs (1947) have shown that a majority of infections may occur in outbreaks due to distinct serological types of *Staph aureus* During the outbreak the epidemic strain is found in a multiplicity of sources in the hospital It occurs in the lesions of clinically infected infants, and also in the noses of healthy carriers who include a large proportion of the well infants, mothers and nurses *Staph aureus* contamination of the hands is likely to be present in as many as half of the nasal carriers Commonly the milk of nursing mothers is infected, but this is not thought to be an important source of infection for the infants, it appears that the breast usually receives the infection from an already infected child (Duncan and Walker) The epidemic staphylococcus may be present and viable on the infant's garments and bedding, even after laundering, and in the floor dust and air of the hospital In a few observations made with "settling plates," Elliot, Gilliespie and Holland (1941) and Allison and Hobbs (1947) found *Staph aureus* to be present in the air of the hospital nurseries during outbreaks of pemphigus Allison and Hobbs regarded the degree of air infection as low, they concluded that the main reservoir of infection was the nasal passages of healthy carriers among the nursing staff, and that the main means of spread thence to the infants was probably by contact with the carrier's hands, in addition, infection from infant to infant by the commonly shared bath, towel and laundry was thought likely to play an important part

The present investigation of *Staph aureus* infection in a maternity hospital unit was directed particularly to assessing the extent of infection of the air For various reasons it was anticipated that airborne infection would prove to be of major importance *Staph aureus* has been one of the pathogenic bacteria most commonly found in the air of occupied premises, for instance, in surgical operating theatres (Hart, 1937, 1938, Hart and Schiebel, 1939, Devenish and Miles, 1939, MacDonald, 1940), in surgical and burns wards (Miles *et al*, 1940, Bourdillon and Colebrook, 1946, Colebrook and Cawston, 1948), and in wards of an infants' hospital (Brooks, Wilson and Blackfan, 1942) In the case of other respiratory-tract bacteria which probably spread in the same way as *Staph aureus*, the practice of aseptic nursing procedures for avoidance of contact spread has generally failed to prevent a high incidence of cross-infections in open multi-bed wards , on the other hand, cross-infections have been eliminated where the patients were isolated in single-bed cells designed to prevent airborne spread (Allison and Brown, 1937 , Wright, Shone and Tucker, 1941 , Stalker, Whatley and Wright, 1942 , Chapple, 1942)

CIRCUMSTANCES OF THE INVESTIGATION

The investigation was carried out during sixteen weeks from 12th March to 2nd July 1947, in the maternity unit of a large general hospital in Edinburgh The unit consisted of several rooms opening into a common corridor , it included a mothers' ward (26×16×13 ft of nine beds), a large nursery (30×14×13 ft , of twenty-six cots), a small nursery (18×16×13 ft , of fourteen cots), a small washroom, a babies' changing room, an isolation ward and offices The premises were clean and airy , the floors were of polished wood , the windows were large, of part-southerly exposure and usually kept open There was no appearance of overcrowding Most of the beds in the mothers' ward and over half of the cots in each nursery were occupied during the period of the investigation The day and night nursing staffs together usually totalled twelve The nurses wore masks and gowns when attending the babies The babies were changed seven times a day or oftener, and were taken at four-hourly intervals to the mothers' ward for nursing In the course of medical examinations, toilet, bed-making, serving meals and domestic cleaning, the ward and nurseries were entered frequently by doctors, nurses and ward maids , visitors were admitted only to the mothers' ward Mother and child remained in hospital for about ten days

During the spring of 1947 the maternity unit reported a high incidence of *Staph aureus* infections , this prevalence continued throughout the period of the investigation Among the infants, septic skin lesions and conjunctivitis were especially common, and there was one fatal case of staphylococcal pneumonia Among the mothers, there were cases of breast abscess, boils, conjunctivitis and Cæsarian wound infection due to *Staph aureus* The taking of nasal swabs on one occasion revealed a high incidence of healthy carriers , 2 out of 7 nurses and 11 out of 26 babies carried *Staph aureus* in the nostrils

EXPERIMENTAL METHODS

Two methods were used for examining the bacterial content of the air , namely, exposure of culture plates to direct sedimentation of infected particles (" settling plates "), and use of the slit sampler of Bourdillon, Lidwell and Thomas (1941) The " settling plates " presented 10 sq in of culture medium surface , they were left open on a table in the centre of the room The slit sampler was run at 1 cu ft per minute, with a slit-plate distance of 2 mm , it was placed centrally in the room at about 3 ft above the floor No person was allowed to approach closely to the slit sampler, except the observer at the time of changing plates

Four different culture media were used (1) nutrient agar (1 per cent. meat extract, 1 per cent peptone, ½ per cent sodium chloride and 2 per cent agar), (2) blood agar (nutrient agar with 5 per cent horse blood), (3) MacConkey agar (2 per cent peptone, ½ per cent sodium taurocholate, 1 per cent lactose, 2 per cent agar and neutral red to tint), and (4) salt-milk agar (nutrient agar with 20 per cent milk and 7 per cent sodium chloride) The batch of MacConkey agar used gave good growth of *Staph aureus* with enhancement of pigmentation, and inhibited growth of many other airborne species Similarly, the salt-milk agar was partially selective for *Staph aureus* because of its 7 per cent salt content (Chapman, 1945) and enhanced pigmentation because of its milk content (Christie and Keogh, 1940) Plates were incubated aerobically at 37° C for twenty-four hours and then left at room temperature for a further twenty-four hours The colonies were counted with the aid of a plate microscope All golden-coloured colonies which resembled *Staph aureus* were subcultured and tested for coagulase production , only the coagulase positive strains were recorded as *Staph aureus*

TWENTY-FOUR HOURS SETTLING PLATE OBSERVATIONS

Observations with settling plates exposed for a continuous twenty-four-hour period were made on each of forty days chosen at intervals between 12th March and 2nd July , a MacConkey plate and a salt-milk agar plate were exposed in each room *Staph aureus* was thereby recovered from the air of the maternity unit on thirty-six of the forty days on twenty-six of forty days in the large nursery, on twenty-six of forty days in the small nursery, on eleven of fourteen days in the mothers' ward and on fourteen of twenty-three days in the washroom The number of *Staph aureus* colonies obtained was small, seldom more than two or three per plate , the number did not vary much between the different rooms, nor between different weeks throughout the investigation

SLIT SAMPLER AND SETTLING PLATE OBSERVATIONS DURING MORNINGS

On seven days during the investigation period, parallel observations with slit sampler and settling plates were made during the morning In one of the nurseries, or in the mothers' ward, air sampling was carried out continuously from 7 30 a m till 2 p m , the period of the day when the wards were busiest and the air infection presumably highest MacConkey plates were used in the slit sampler on six occasions, and nutrient agar plates on the seventh , 25 cu ft of air was taken on to each plate in the slit sampler during the first twenty-five minutes of each successive half-hour throughout the morning Concurrently, a blood-agar settling plate was exposed during each twenty-five-minute period As a rough measure of the amount of activity in the ward during the taking of each sample, a record was made of the number of " entrances," that is the number of occasions on which a doctor, nurse or maid entered the ward

The results of the seven experiments are summarised in Table I,

TABLE I

Air Contamination with Staph aureus and other Bacteria in a Maternity Hospital (Shows for each day the average number of bacteria carrying particles per cu ft of air taken by the slit sampler, and the average number recovered per 10 *sq in settling plate per hour*)

Date of experiment —	18/6	25/6	14/5	21/5	28/5	4/6	2/7	Overall Average
Room —	Large Nursery	Large Nursery	Small Nursery	Small Nursery	Mothers Ward	Mothers Ward	Mothers Ward	
Number of entrances	136	55		51	100	80	114	
Amount of ventilation —	Medium	Medium	Medium	Great	Very Great	Great	Medium	
Slit sampler * —								
Cubic ft. of air sampled	325	300	300	300	325	275	300	
All bacteria per cu ft	5 9	5 2	5 1	1 5	9 2	10 6	14 2	7 4
Staph aureus per cu ft	0 040	0 037	0 027	0 010	0 100	0 040	0 020	0 04
Settling plates † —								
Plate hours exposure	5½	4½		5	5	4½	5	
All bacteria per plate hour	43	30		21	110	87	132	71
Staph aureus per plate hour	0 9	0 2		0 2	1 0	0 24	0 2	0 46

* MacConkey agar plates except in experiment 2/7 when nutrient agar was used
† 10 sq in blood agar plates

and the detailed observations for one experiment in the large nursery are shown in Table II In the seven days a total of 2125 cu ft of air was examined with the slit sampler , this was found to contain eighty-five particles carrying *Staph aureus*, an average of 0 04 per cu ft Some *Staph aureus* were found present in the air in each room and on each day , the average numbers for the different days varied from 0 01 to 0 10 per cu ft The results of the examinations with the settling plates were in general agreement with the slit sampler results , *Staph aureus* was recovered from the air on all of the seven days, the overall average recovery rate being 0 46 infected particles per 10 sq in plate per hour

The amount of *Staph aureus* air contamination did not show obvious correlation either with the concurrent amount of activity as measured by the number of " entrances," or with the amount of ventilation as judged by the extent of window opening and the sensation of draught The heaviest *Staph aureus* air contamination occurred on the occasion when the ventilation was greatest namely, in the mothers' ward on 28th May, a breezy and sunny day when all windows were fully open and a strong draught was felt almost continuously

The *Staph aureus* colonies comprised 0 70 per cent of all colonies on the MacConkey plates exposed in the slit sampler (six experiments) and 0 68 per cent of all colonies on the blood-agar settling plates (six experiments)

DISCUSSION

Throughout sixteen weeks when infections were prevalent, *Staph aureus* was found to be present almost constantly in the air of the maternity ward and nurseries The number of infected particles found in the air was small Nevertheless, because of the large volume of air respired, the amount of air infection observed was sufficient to ensure that each adult and baby would inhale *Staph aureus* on many occasions while in the hospital The average morning air contamination was 0 04 *Staph aureus*-carrying particles per cu ft If in each day the air contamination continued at this level for the fourteen daytime hours and at zero for the ten quiet night hours, then, on average, about twelve *Staph aureus*-carrying particles would have been inhaled per day by an adult respiring 500 cu ft of air, and one *Staph aureus*-carrying particle by a newborn child respiring 44 cu ft (Nelson, 1946)

The settling plate results give a measure of the danger from sedimentation of airborne infected particles on to the face and other exposed parts of the baby A *Staph aureus*-carrying particle would be received

TABLE II

Air Contamination with Staph aureus and other Bacteria in Large Nursery during Morning of 18th June

Time	"Entrances"	Colonies per 25 cu ft of Air by Slit Sampler *		Colonies per 25 Minutes per 10 sq in Settling Plate †	
		All Bacteria	*Staph aureus*	All Bacteria	*Staph aureus*
07 30 25	15	180	0	18	0
08 00 25	20	160	0	26	0
08 30 55	17	140	0	23	0
09 00 25	7	196	0	33	1
09 30 55	6	120	0	6	0
10 00 25	12	200	0	26	1
10 30 55	5	132	1	22	1
11 00 25	11	216	0	19	0
11 30 55	13	204	1	18	0
12 00 25	14	154	4	23	1
12 30 55	7	53	0	14	0
1 00 25	7	48	1	5	1
1 30 55	2	104	6	6	0

* MacConkey agar plates
† Blood agar plates

per 10 sq in of exposed surface in each two or three hours during a morning in the nursery

If a single infected particle, containing perhaps from 1 to 100 *Staph aureus* cells, be sufficient to initiate infection, then the amount of *Staph aureus* air contamination discovered in the hospital was clearly enough to account for a very high incidence of infection among the inmates, even for universal infection of the babies within a day or two of birth On the other hand, it is sometimes argued that initiation of infection normally requires contamination by a large number of bacteria, and can seldom follow receipt of the small numbers which are transmitted by the air , then, it is suggested that the large number of bacteria which constitute an adequate infective dose will be transmitted most commonly by contact and handling However, there are reasons why one should not too readily assume that especially large numbers of pathogenic bacteria are likely to be transmitted by contact The experiments of Ostermann (1908) have shown that only a very small proportion, usually less than 1 in 10,000 of the bacteria on a contaminated hand are transferred to a clean hand by the act of handshaking *In the present investigation a series of " handling " tests* were made with two profuse nasal carriers of *Staph aureus*, each test on a different day The surface of a culture plate was heavily handled by the carrier with the fingers, knuckles and palmar eminences of both hands *Staph aureus* was obtained on the plate in most tests in thirteen of fifteen tests with one carrier and in five of six tests with the other However, the number of *Staph aureus* colonies obtained was small, it varied from 1 to 112 per plate and averaged only 13 per plate These observations suggest that as a rule only small numbers of *Staph aureus* will be transmitted by contact with the contaminated hands of nasal carriers Heavier infection by handling may well be caused by " deep " skin carriers, persons whose hands are colonised and not merely contaminated by the staphylococci (Gillespie, Devenish and Cowan, 1939), however, such skin carriers are relatively uncommon

The anterior nares constitute the main natural habitat of *Staph aureus* , presumably this is the site most favourable to the initial establishment of colonisation It is thus suggested that the spread of *Staph aureus* is in the first place mainly airborne, a small number of staphylococci being inhaled, caught in the anterior nares and there greatly multiplied From the infected nose of an infant, large numbers of staphylococci may then be spread during bathing and toilet to skin abrasions, the conjunctiva and other susceptible parts of the body where they give rise to clinical infections

The main source of the staphylococcal contamination of the hospital air was probably dust from bedding (Bourdillon and Colebrook, 1946), from personal clothing (Duguid and Wallace, 1948) and from handkerchiefs (Dumbell, Lovelock and Lowbury, 1948) In view of our previous finding that very little *Staph aureus* contamination of air was produced by the sneezing of nasal carriers (Duguid and Wallace, 1948), we conclude that the air infection was not due in any important degree to the secretion droplet-nuclei described by Chausse (1913) and Wells (1934)

SUMMARY

(1) THROUGHOUT sixteen weeks during an outbreak of *Staph aureus* infections in a maternity hospital, the bacterial content of the air in two nurseries, a mothers' ward and a washroom was repeatedly observed by use of a slit sampler and of settling plates

(2) Air contamination with small numbers of *Staph aureus* was present almost constantly, being found in at least one room on forty-three out of forty-seven days on which examinations were made

(3) During seven mornings a total of 2125 cu ft of air was taken by the slit sampler from the nurseries and ward On average this contained 0 04 *Staph aureus*-carrying particles per cu ft, these comprising about 0 7 per cent of all bacteria-carrying particles collected On this basis it was calculated that while residing in the hospital an infant would inhale about one *Staph aureus*-carrying particle per day, and an adult about a dozen

(4) Observations made with settling plates showed that during the mornings *Staph aureus* particles were falling from the air at the average rate of 0 46 particles per 10 sq in per hour

(5) Experiments were made in which culture plates were heavily handled by nasal carriers Only small numbers of *Staph aureus* colonies were obtained on each plate It was concluded that *Staph aureus* would not be transmitted in much larger numbers by contact and handling than by the air

We are indebted to Professor T J Mackie for his interest and advice

REFERENCES

ALLISON, V D, and BROWN, W A (1937), *Journ Hyg*, 37, 153

ALLISON, V D, and HOBBS, B C (1947), *Brit Med Journ*, 2, 1

BOURDILLON, R B, and COLEBROOK, L (1946), *Lancet*, 1, 561 and 601

BOURDILLON, R B, LIDWELL, O M, and THOMAS, J C (1941), *Journ Hyg*, 41 197

BROOKS, G L, WILSON, U, and BLACKFAN, K D (1942), "Ærobiology," *Amer Assoc Adv Sci*, Publ No 17, p 228

CASS, J M (1940), *Arch Dis Child*, 15, 85

CHAPMAN, G H (1945), *Journ Bact*, 50, 201

CHAPPLE, C C (1942), "Ærobiology," *Amer Assoc Adv Sci*, Publ No 17, 251

CHAUSSÉ, P (1913), *C R Acad Sci*, 156, 638

CHRISTIE, R, and KEOGH, E V (1940), *Journ Path Bact*, 51, 189

COLEBROOK, L, and CAWSTON, W C (1948), *M R C*, Spec Rept Ser, No 262, p 233

DAVENISH, E A, and MILES, A A (1939), *Lancet*, 1, 1088

DUGUID, J P, and WALLACE, A T (1948), *Lancet*, 2, 845

DUMBELL, K R, LOVELOCK, J E, and LOWBURY, E J (1948), *Lancet*, 2, 183

DUNCAN, J T, and WALKER, J (1942), *Journ Hyg*, 42, 474

ELLIOT, S D, GILLIESPIE, E H, and HOLLAND, E (1941), *Lancet*, 1, 169

GILLIESPIE, E H, DEVENISH, E A, and COWAN, S T (1939), *Lancet*, 2, 870

HART, D (1937), *Arch Surg*, 34, 874

HART, D (1938), *Arch Surg*, 37, 521

HART, D, and SCHIEBEL, H M (1939), *Arch Surg*, 38, 788

LUDLAM, G B (1947), " Health Bulletin," *C M O Dept Hlth Scot*, 5, nos 3 5

MACDONALD, K (1940), *Amer Journ Hyg*, 31b, 74

MILES, A A, SCHWABACHER, H, CUNLIFFE, A C, ROSS, J P, SPOONER, E T C, PILCHER, R S, and WRIGHT, J (1940), *Brit Med Journ*, 2, 895

NELSON, W E (1946), *Textbook of Pediatrics*, Philadelphia p 212

OSTERMANN, A (1908), *Z Hyg*, 60, 375

STALKER, W S, WHATLEY, E, and WRIGHT, J (1942), *Journ Hyg*, 42 231

WELLS, W F (1934), *Amer Journ Hyg*, 20, 611

WRIGHT H D, SHONE, H R, and TUCKER, J R (1941), *Journ Path Bact* 52, 111

NOTES

Royal College of Physicians of Edinburgh

I BEG to announce that the College at the Annual Meeting held on Thursday, 6th December, elected Dr William Alister Alexander as President, and Drs Leybourne Stanley Patrick Davidson, Douglas James Acworth Kerr, Douglas Nairn Nicholson, Ranald Malcolm Murray-Lyon, James Gilbert Murdoch Hamilton and Thomas Anderson as Members of Council, and that thereafter the College elected Dr Douglas James Acworth Kerr as Vice-President

The Council of the College elected the following Office-Bearers —John Alastair Bruce, T D, *Treasurer*, J Halliday Croom, M B, *Secretary and Registrar*, D M Lyon, M D, *Honorary Librarian*, Alexander Macfie, W S, *Clerk*, H J B Dunlop, C A, *Auditor*

NEW BOOKS

Any Questions? From the *British Medical Journal* Pp xii+240 London British Medical Association 1951 Price 7s 6d

This booklet is a collection of the more interesting questions and answers taken from the *British Medical Journal* It is grouped systematically, each section containing a brief summary of recent advances, views on controversial problems and explanatory notes on medical terminology This book is ideally suited for bed-time browsing, the only drawback being its brevity, but this year's popularity may well stimulate the editors to correct this rare fault in future volumes

Clinical Urography—An Atlas and Textbook of Roentgenologic Diagnosis By WILLIAM F BRAASCH, M D, and JOHN L EMMETT, M D Pp v+736, with 1361 figures London W B Saunders Company Price 125s net

This excellent publication is precisely what its sub-title claims it to be

From the wealth of the radiological files of the Mayo Clinic the authors would appear to have included examples of each and every variant of normal and pathological urogram These are reproduced with a clarity of illustration and description which makes this a most readable and instructive volume

The book is planned on a pathological rather than an anatomical basis, and each chapter concludes with an extensive but deliberately selected bibliography The text includes detailed notes of the technique employed in the various methods of examination by which the radiograms were obtained These methods include demonstrations of the radiological value of vascular patterns obtained by aortography and the examination of the genital tract in the male

This is a most comprehensive volume, and is one which, in the opinion of the reviewer, fills a long-felt gap in the urologist's library It is not only a valuable textbook for the post-graduate student but is a complete guide and reference work on the subject for the practising surgeon

The volume is, of course, produced and bound in the manner we have grown to expect of the W B Saunders Company

Child Care By AGATHA H BOWLEY Pp xix+203 Edinburgh E & S Livingstone Ltd 1951 Price 10s 6d net

Any person interested in the care of children will appreciate Agatha Bowley's new book In it she gives an admirable account of the various ways in which illegitimate children may be brought up, together with details of the relevant Acts of Parliament and a useful bibliography

Health and the Citizen By JOSEPH V WALKER Pp 158 London Hollis & Carter 1951 Price 10s 6d

This is a thoughtful and thought-provoking book written by a medical officer of health who has learnt from his own experience that medicine is concerned no less with Welfare than with Health The author writes of the family as the social unit and considers those factors which, in an industrialised, urbanised society, affect its health and welfare He has wise things to say concerning the problems created by the ageing of the population and considers work and play, neighbourhood and community, in their medical aspects His therapy for very many of the more serious sicknesses from which a modern society suffers is derived not from the *British Pharmacopœa* but from the Bible, and not from the Old Testament but from the New

The Physician as a Man of Letters, Science and Action By T K MONRO Pp 259 Edinburgh E & S Livingstone 1951 Price 25s

This attractive volume is virtually a dictionary of eminent medical men who have distinguished themselves in various fields, and is a revised and enlarged edition of a book which appeared in 1933 It does not claim to be complete, and the reader will seek in vain for Paracelsus, Vesalius and Harvey On the other hand, he will make the acquaintance of many new friends, rescued by the author from an unaccountable obscurity Most of the potted biographies consist merely of a few sentences, but it is not surprising that Professor Monro allows his pen to run on, as he deals with such giants as Sir Thomas Browne and Sir William Osler The arrangement of categories has been accomplished with much skill they are twenty-five in number, proceeding from poets and dramatists, through literature, law, philosophy, science, sport and even crime, until at length we meet " Some students of medicine who never qualified," among them Darwin, Galileo and Goethe It is interesting to find among the literary doctors, Harry Roberts, Dan McKenzie, and that favourite of those who were boys in the nineties, Gordon Stables This is certainly not a book which can be read from cover to cover Yet it is not merely a reference work, and it is never dull An ideal bedside book, it will enable many a tired doctor to end the day in company with the immortals, even though the claims of some of them to immortality are hardly enviable Among the pirates is Thomas Dover, among the criminals, Hawley Harvey Crippen, and, although it seems hardly fair to place him in such company, Alexander Cameron of Lochiel Although not illustrated, the volume is well produced, and there is a good biographical index as well as a general index

Patterns of Disease as a Basis of Physiologic Pathology By FRANK L APPERLY, M A, M D, D SC, F R C P Pp xiii+456, with 87 illustrations London J B Lippincott & Company 1951 Price 63s net

The author has written a book combining applied physiology with pathology Each disease is presented in its initial stages and each step in its progression is followed The biochemical changes are discussed first and then the altered function, altered anatomy and the final cure or death The compensatory mechanisms adopted by the body throughout these diseases are discussed fully yet concisely The diagrams are clear and the illustrations excellent

This book can be highly recommended to both undergraduate and post-graduate

Brompton Hospital Reports, volume XIX 1950 Pp vii+199 To be had from the Secretary, Brompton Hospital, London, S W 3 Price 12s 6d

This volume consists of eighteen papers most of which have already appeared in recent medical journals Two, however, are published here for the first time These are an article on " Education and Management of the Sanatorium Patient " and a valuable ten year follow up of patients with empyema complicating artificial pneumothorax Most of the papers deal with diseases of the chest This valuable publication is a great credit to the Staff of the Brompton

Systemic Ophthalmology Edited by ARNOLD SORSBY Pp xiv+712, with 38 colour plates London Butterworth & Co (Publishers) Ltd 1951 Price 84s net

This book, the work of thirty-four contributors, may best be described as a collection of monographs covering a variety of subjects in the wide field of ophthalmology in relation to general medicine

Although, as is stated in the preface to this volume, the field covered by systemic ophthalmology has probably become too large to be covered satisfactorily by either a physician or by an ophthalmic surgeon, the alternative selected in this case, namely to seek the collaboration of more than thirty authors, can hardly fail to result in a lack of continuity of thought and outlook, features which were so essential a part of the great medical textbooks of the past While certain sections of this book are authorative summaries of present-day knowledge, others are more superficial in their approach and detract from the value of the book as a whole The section on the relationship of prematurity to ocular anomalies in post-natal development is an excellent summary of the problems which may confront the clinician, particular attention being paid to the subject of retrolental fibroplasia Chronic bacterial infections such as tuberculosis, sarcoidosis and brucellosis are discussed in a chapter which is not only authoritative but most beautifully illustrated, and the chapters on endocrine disorders and cranio-cerebral injuries, as they affect the eyes, are also excellent

There is no doubt that this well-produced volume contains much that will be of interest and value both to the physician and to the ophthalmic surgeon

The Versatile Victorian By ZACHARY COPE, M D Pp xi+179, illustrated London Harvey & Blythe 1951 Price 12s 6d

Sir Henry Thompson, Bart, lived from 1820 to 1904, thus covering the whole of the Victorian era He was born of a middle-class family and was unequipped with the advantages gained from education at a public school or University, yet rose by his own ability and effort to a position in which he mingled with ease with the most distinguished people of his generation and he left his mark upon the Victorian Age

Thompson turned to surgery and specialised in urology The author traces his career from student days at University College Hospital through the various stages of advancement till he became a leading consultant and the friend of royalty This versatile surgeon had many interests other than his profession and it is necessary to deal with these separately Thus there are chapters on the connoisseur and dilettante, the artist, the writer, the traveller and the social reformer The story covers a period of wonderful advances which revolutionised surgery and raised the status and importance of the profession It also gives a wonderful picture of Victorian England and the great men of the day The author is to be congratulated on the production of a first-class biography of an outstanding surgeon and a man of many parts

Atlas of Histologic Diagnosis in Surgical Pathology By KARL T NEUBUERGER, with a section on Exfoliative Cytology by WALTER T WIKLE Pp x+460, with 880 illustrations London Baillière, Tindall & Cox 1951 Price 84s net

The histopathologist is continually being confronted with new problems for reasons such as rarity of the disease, unfamiliarity with the field or unusual nature of the cellular reaction Consequently, a series of photomicrographs with appropriate legends covering routine surgical practice so widely as is achieved in this volume will find acceptance with the histopathologist at all stages in his career Reference is facilitated by a regional arrangement and ample index, while a section on exfoliative cytology adds topical prestige Photography and reproduction are good, but a future edition might with advantage include suitably selected subjects in colour

NEW EDITIONS

Oral and Dental Diseases By HUBERT H STONES, M D, M D S, F D S, R C S Second Edition Pp xix+1011, with 959 illustrations, 91 in colour Edinburgh E & S Livingstone Price £5

This excellent book, first printed in 1948, is now deservedly in its second edition While the main features remain as before, all the chapters have been revised and brought up to date by the addition of new material and by the inclusion of the latest references The chapter on the etiology of dental caries has been rewritten and this difficult subject is now presented in a form which is comprehensive and concise

The chapters on malocclusion of the teeth, maldevelopment of the jaws, stomatitis and allied diseases of the oral mucosa, odontomes and tumours, have all been amended and partially rewritten and there is little doubt that a considerable improvement has resulted

One great advantage of the book is that it is written in simple language and is, therefore, readily understandable by undergraduate students The fact that the whole field of oral pathology has been adequately covered makes it also suitable for post graduate students studying for higher qualifications

The publishers deserve to be complimented on the exceedingly high standard of their work, which has added greatly to the value of the book

Clinical Hematology By MAXWELL M WINTROBE, M D, PH D Third Edition Pp 1048, with 220 illustrations and 17 plates London Henry Kimpton 1951 Price 90s net

A new edition of " Wintrobe " has come to mean quite an event in hæmatology and it is a pleasure to find this splendid textbook brought once again so completely abreast of the times Though enlarged by 180 pages, it retains its freshness as a balanced and critical presentation of the growing field of knowledge in blood disorders, and the important advances made since the last edition in 1946 have been woven into, rather than merely added to, the text Though essentially American in outlook, the extensive bibliography adequately covers the world-wide literature, and the volume remains a standard work for all interested in hæmatology

Principles and Practice of Obstetrics By J P GREENHILL and J B DE LEE Pp x+1020, with 1140 on 864 figures London W B Saunders Company 1951 Price 60s

Under the authorship of J P Greenhill, this edition has been carefully revised so that its reputation, established in the days of the late J B De Lee, as an up to date book of reference, rather than a textbook, is maintained Numerous authorities have contributed sections on their special subjects, others have revised chapters for the author, or supplied data A bibliography is appended to each chapter Extensive summarisation of original articles, such as Sheehan's on Shock, duly acknowledged, are incorporated in the text, yet throughout, the author expresses his personal opinion on controversial matters, or his preference for a given technique when a choice is available With changing views and practices, it is difficult to know what to retain or discard in a new edition, and it is interesting to note that the passage of a metreurynter into the uterus in the treatment of placenta prævia is still illustrated and described in detail, albeit the text is in the small print used elsewhere for historical notes

Beautifully reproduced figures, of which 194 are in colour, liberally illustrate the text and are, as before, a valuable feature of this work

BOOKS RECEIVED

BAILEY, HAMILTON, F R C S (ENG), F A C S, F I C S, F R S E Emergency Surgery Sixth Edition (*John Wright & Sons, Ltd, Bristol*) 21s Post 5d

BECK, ALFRED C, M D Obstetrical Practice Fifth Edition (*Baillière, Tindall & Cox, London*) 7s 6d net

BERNSTEIN, L, B SC, M R C S, L R C P, and WEATHERALL, M, M A, D M, B SC Statistics for Medical and Other Biological Students (*E & S Livingstone, Ltd, Edinburgh*) 18s net

BETT, W R Osler The Man and the Legend (*Wm Heinemann, Medical Books, Ltd, London*) 15s net

CADE, Sir STANFORD, K B E, C B, F R C S, M R C P, F F R (HON) Malignant Disease and its Treatment by Radium Volume IV Second Edition (*John Wright & Sons, Ltd, Bristol*) 63s Post 1s 1d

CARTWRIGHT, F F The English Pioneers of Anæsthesia (*John Wright & Sons, Ltd, Bristol*) 21s Post 7d

Edited by CECIL, RUSSELL L, M D The Specialties in General Practice (*W B Saunders Company, London*) 72s 6d

DERBES, VINCENT J, M D, F A C P, and WEISS, THOMAS E, M D Untoward Reactions of Cortisone and ACTH (*Blackwell Scientific Publications, Oxford*) 8s 6d net

DUKE ELDER, Sir STEWART, K C V O, M D, LL D, D SC (ST AND), PH D (LOND), M D, F R C S, HON D SC (NORTHWESTERN), D M (UTRECHT) F R C S (EDIN), F A C S Volume V (*Henry Kimpton, London*) 90s net

GEFFEN, DENNIS H, M D, D P H, and TRACY, SUSAN, M R C S, L R C P, D P H Hygiene, Infectious Diseases and Dietetics (*Longmans, Green & Co, London*) 9s 6d net

HALL, I SIMSON, M B, CH B, F R C P E, F R C S E Diseases of the Nose, Throat and Ear Fifth Edition (*E & S Livingstone, Ltd, Edinburgh*) 18s net

HERXHEIMER, HERBERT G J, M D FRANKFORT, L R C P ED, L R C S ED, L R F P S GLAS The Management of Bronchial Asthma (*Butterworth & Co (Publishers), Ltd, London*) 22s 6s net

HOLMES, GORDON, M D, F R S Introduction to Clinical Neurology Second Edition (*E & S Livingstone, Ltd, Edinburgh*) 12s 6d net

Edited by JONES, F AVERY, M D, F R C P Modern Trends in Gastro Enterology (*Butterworth & Co (Publishers), Ltd, London*) £5, 5s net

KOLMER, JOHN A, M D, D P H, SC D, F A C P, SPAULDING, EARLE H, PH D, and ROBINSON, HOWARD W, PH D Approved Laboratory Technic Fifth Edition (*H K Lewis & Co, Ltd, London*) 90s net

KRANTZ, JOHN C, JR, and CARR, C JELLEFF The Pharmacologic Principles of Medical Practice (*Baillière, Tindall & Cox, London*) 76s 6d net

KRUSEN, FRANK H, M D Physical Medicine and Rehabilitation for the Clinician (*W B Saunders Company, London*) 32s 6d

LEVINSON, SAMUEL A, M S, M D, PH D, and MACFATE, ROBERT P, CH B, M S, PH D Clinical Laboratory Diagnosis Fourth Edition (*Henry Kimpton, London*) 84s net

MCKENZIE, WILLIAM, M B, B CHIR (CANTAB), F R C S (ENG) Ear, Nose and Throat Diseases (*E & S Livingstone, Ltd, Edinburgh*) 9s net

OLIVER, LESLIE C, F R C S ENG Essentials of Neurosurgery (*H K Lewis & Co, Ltd, London*) 25s net

PICKWORTH, F A, M B, B S, B SC New Outlook on Mental Diseases (*John Wright & Sons, Ltd, Bristol*) 60s Post 11d

POTTER, EDITH L, M D, PH D Pathology of the Fetus and the Newborn (*The Year Book Publishers, Inc, Chicago, U S A*) $19 00

PURVES STEWART, JAMES, K C M G, C B, M D EDIN, F R C P, and WORSTER DROUGHT, C, M A, M D CANTAB, F R C P The Diagnosis of Nervous Diseases Tenth Edition (*Edward Arnold & Co, London*) 58s net

ROBERTS, LLYWELYN, M D, M R C P, D P H, Assisted by SHAW, KATHLEEN M, M B E A Synopsis of Hygiene (*J & A Churchill, Ltd, London*) 42s net

SAMUEL, ERIC, M D (LOND), F R C S (ENG), F F R (LOND), D M R E (CAMB) Clinical Radiology of the Ear, Nose and Throat (*H K Lewis & Co, Ltd, London*) 70s net

SAND, RENE The Advance to Social Medicine (*Staples Press, Limited, London*) 42s net

Edited by SELLORS, T HOLMES, M A, D M, M CH, F R C S, and LIVINGSTONE, J L, M D, F R C P Modern Practice in Tuberculosis Volumes I and II (*Butterworth & Co (Publishers), Ltd, London*) £7, 7s 2 volumes

Edinburgh Medical Journal

May 1952

CLEARANCE TESTS OF RENAL FUNCTION

By C P STEWART, D Sc , Ph D

INTRODUCTION

IT is probably fair to say that clearance tests provide the most potent means at present available for the study of the normal mechanism of urine secretion as well as of abnormal renal function This does not deny the fundamentally important contributions which other methods, often vastly different in character, have made in the past and may well continue to make in the future , but it emphasises the peculiar advantages of clearance tests for the study of renal function in living man Nevertheless, clearance tests have their limitations (sometimes ill-defined or insufficiently appreciated) so that interpretation of the results of such tests can be difficult and may even be misleading *The aim of this lecture is to outline the basis and scope* of clearance tests, and to point out some of the difficulties in technique and interpretation which at present limit their usefulness It is an aim too ambitious for a single lecture because the subject is vast and rapidly growing , nor is any finality in sight with respect either to *technique or to interpretation , yet I may hope at least to provide* a bare outline with some hints which may indicate how the details may be filled in And for a very full and masterly summary of the whole subject, may I at once refer you to Homer Smith's classic book on *The Kidney , Structure and Function in Health and Disease* *Had Homer Smith not, himself, been one of the great builders of our* modern corpus of knowledge of renal function, we would still owe him an immense debt of gratitude for that book alone

MODERN THEORY OF RENAL FUNCTION

It is desirable to begin by summarising the modern views on the mechanism of urine secretion since these views have been reached by considering evidence drawn from many, varied, sources and since they must, so long as they remain acceptable in the light of all existing evidence, be the basis for the interpretation of clearance measurements

The glomeruli possess, in the endothelium of the glomerular capillaries and the basement membrane, a filter which offers no obstruction to the passage of small molecules of non-electrolytes or small ions (except such as is imposed by the Donnan equilibrium) but retains macro-particles such as protein ions, fat droplets, and, *a fortiori*, blood cells This filter, by a physical process, allows the formation of the " glomerular filtrate," in which the filtered substances are present in the same concentrations per unit volume of water as in the original plasma, except where the Donnan effect has interfered

Glomerular filtration is thus envisaged as a *passive* process of which the rate depends on the area of the filter (the number of active glomeruli), the supply of material (rate of plasma flow to the active nephrons) and the filtration pressure (depending on the blood pressure, the osmotic pressure of the non-filterable particles, etc) , the separation achieved by the glomeruli thus depends for its driving force on cardiac activity The *active* work of the kidney itself is done during the passage of the glomerular filtrate through the tubules There some of the constituents are reabsorbed (*e g* water, sodium, chloride, glucose, urea, etc) whilst others are increased in concentration by actual tubular excretion (*e g* creatinine, potassium) These activities are not continuous throughout the whole length of the tubule Thus the proximal tubule reabsorbs water along with sodium ions (and their equivalent of chlorine ions) so that tonicity and *p*H remain unaltered , concentration and acidification of the urine occur in the distal tubule Such finer points as these, and the question of the mechanism, which may perhaps involve enzyme activity, of the transport of molecules into and out of the tubule cells, are not yet of immediate importance to a consideration of renal clearance, however much they may become so in the future and however essential they may be, even now, for a full understanding of renal function

RENAL CLEARANCE AND ITS MEASUREMENT

The concept of clearance, particularly as it has recently been developed, was implicit in the earlier work of Rehberg and even in the formulæ of Ambard, Addis and others designed to express the excretory capacity of the diseased, in relation to the normal, kidney These workers, dissatisfied with the crude tests of renal function based solely on urine analyses, and realising the dependence of the rate of excretion of (*e g*) urea on the concentration in the blood had attempted to find some means of formulating the relationship Indeed Addis conceived the idea that part of the blood flowing through the kidney might be regarded as passing unchanged, whilst the urea was completely removed from the remainder Their efforts were further developed by Van Slyke and his collaborators who were the first to employ the term " clearance " which they defined as the volume of blood which must be cleared of urea to provide the amount excreted in the urine in one minute The term " clearance " is perhaps analogous to the term " vitamin " the invention of which was so important in focussing attention on the " accessory food factors " which Hopkins had previously described

Since it is the plasma which is filtered by the glomeruli, and since there is rarely (if ever) sufficiently free and rapid interchange between the blood cells and the plasma for the former to be appreciably "cleared" during passage through the kidney, it is now customary to consider *plasma* clearances and to extend the term to describe the excretion of any substance Obviously the clearance can only be virtual and not actual, for all the blood flowing through the kidney is partially cleared instead of some of the blood being completely cleared as the definition suggests It is perhaps preferable, therefore, while retaining the well-established term, to define it as the rate of excretion of the test substance in relation to the concentration of that substance in the plasma

With either definition, if V is the volume of urine produced per minute, U_x the concentration of substance x per ml of urine and Px the concentration per ml of plasma, the amount of x excreted in one minute is U_xV and this amount is contained in $\frac{U_xV}{P}$ ml of plasma, so that this final expression represents the *plasma clearance* of x

The determination of plasma clearance demands the measurement of V, U_x and P_x It is necessary to obtain V by collecting urine over a not very prolonged, measured, period of time, the bladder being completely emptied at the beginning and end of the period, this necessity has led to the very general use of catheterisation with careful saline rinsing of the bladder During this collecting period, P_x must be constant or must alter in such a way that its mean value during the period can be calculated, this has led to the practice, when dealing with "foreign" substances of giving an intravenous "priming" injection of the test substance and thereafter maintaining a constant P_x by infusion at constant rate These technical procedures militate against the wide use of clearance determinations except for research purposes and, with the object of developing procedures more suitable for routine diagnostic purposes, many attempts have been made to simplify the technique One of these will be discussed later Where it is desired to measure the clearance of a normal urine constituent (*e g* urea) of which the plasma concentration can be induced to remain nearly constant over a long period, it usually suffices to collect urine over so long a time (*e g* 60 for 120 mins) that errors due to incomplete voluntary emptying of the bladder are minimised, and the simple technique of the "Van Slyke Urea Clearance Test" is satisfactory for ordinary purposes

THE SIGNIFICANCE OF CLEARANCE MEASUREMENTS

The "maximal" $\left(\frac{UV}{B}\right)$ and "standard" $\left(\frac{U\sqrt{V}}{B}\right)$ urea clearance formulæ of Van Slyke and his collaborators suffice to give useful rmation concerning the renal functional efficiency, although the latter of these expressions is somewhat artificial, it does not represent a real clearance but only an approximate prediction of what the clearance would be if $V = 1\cdot 0$, based on the assumption that for values of V below 2 0 c c /min, the clearance is proportional to $\sqrt{V}$

Measurement of the urea clearance, or indeed the measurement of the clearance of any substance can, by itself, give no information about the mechanism by which the test substance is excreted or, consequently, about the efficiency of the individual parts of the mechanism That becomes possible only if a standard of reference can be found—a clearance measurement which assesses one single part of the excretory mechanism Since glomerular filtration is an essential step in the excretion of every substance however it may be treated in the tubules, it is measurement of the glomerular filtration rate which is fundamental to the interpretation of all clearance measurements Briefly, it is obvious that if a substance can be found to be filtered completely by the glomeruli but to be quite unaffected (whether by reabsorption or active excretion) by tubular activity, the amount of that substance excreted in the urine each minute (UV) is the amount filtered per minute by the glomeruli, and its clearance $\left(\frac{UV}{P}\right)$ therefore represents the volume of plasma filtered per minute—the glomerular filtration rate Equally obviously, any substance having a clearance lower than that of this standard substance must be partly reabsorbed by the tubules, anything with a higher clearance must have been additionally excreted by the tubules It is presupposed that if a substance is reabsorbed by the tubules it is not excreted by them, and conversely that there is no reabsorption of a substance which is excreted by the tubules It is on this basis that clearance tests are currently interpreted The supposition is, however, not universally accepted and it is possible that the observed reabsorption (or excretion) really represents the resultant of both processes, one substance being reabsorbed to a greater extent than it is excreted, whilst another is predominantly excreted

Glomerular Filtration Rate—The first to appreciate this seems to have been Rehberg who, chiefly because it was concentrated in the urine to a greater extent than any other known substance (at that time—1926), recommended creatinine, after administration of a test dose, as a measure of glomerular filtration rate Although there is strong evidence that, in man, creatinine can be excreted by the tubules, the reliability of this substance is still under dispute, and the reference substance most usually employed is inulin This fructose polysaccharide with a true molecular weight of about 5000 and a diffusion coefficient corresponding to an apparent molecular weight of 15,000, was suggested independently by Richards, Westfall and Bott, and by Jolliffe and Smith, its establishment as the generally accepted means of measuring glomerular filtration rate is largely due to Smith and his co-workers

Effective Renal Plasma Flow—It will be necessary at a later stage to discuss the validity of the claim that inulin permits measurement of the glomerular filtration rate but for the moment it may be accepted Consideration of the reasoning which led to appreciation of the circumstances in which glomerular filtration rate can be determined shows that a second standard of reference is at least theoretically possible If there exists a substance which by glomerular filtration supplemented by tubular excretion is completely removed from the plasma during one passage through the kidney, so that all the plasma supplied to the functioning nephrons is "cleared," the clearance of that substance must be equal to the effective renal plasma flow Such a substance, it is claimed, has been found in diodone and in *p*-amino-hippuric acid, provided in each case that the plasma concentration is low (1-5 mg /100 ml) The value of determination of the effective renal plasma flow lies in the power it gives of deciding such questions as whether a lowered glomerular filtration rate is due to deficiency of the filter bed itself or to a defective blood supply

Tubular Excretory Capacity—On this basis other clearance measurements begin to assume importance Thus, if the plasma concentration of diodone is progressively increased, the tubules become unable to excrete all the diodone presented to them until ultimately they are working at maximum capacity and still fail to clear the plasma completely Under these conditions of tubular "saturation" the amount of diodone in the urine per minute ($U_D V$) is equal to the amount filtered by the glomeruli *plus* the maximum amount which the tubules can excrete The contribution of the glomeruli is obviously given by the product of the glomerular filtration rate (which may be taken as the inulin clearance (C_{In}) and the plasma diodone concentration P_D Hence the maximum tubular capacity for excreting diodone (usually termed the "active tubular mass" for diodone and represented by the symbol "T_{mD}") is $U_D V - C_{In} P_D$ In practice it is necessary to modify this expression to allow for the facts that only a fraction (F) of the diodone is free and filterable (the remainder being bound to protein) and that although the concentration P_D is actually determined in plasma, the diodone is actually dissolved in the plasma water which constitutes a fraction (W) of the total volume, with these corrections the formula becomes $T_{mD} = U_D V - FWC_{In} P_D$ Fortunately there is evidence that the T_{mD} reflects the excretory capacity of the tubules for other substances so that its determination is of general as well as specific value

Tubular Reabsorptive Capacity—Similarly, the absorptive capacity for various substances can be found Thus glucose, normally, does not appear in the urine because the tubules are able to absorb the whole of the glucose presented to them by the glomerular filtrate ($C_{In} P_G$ per minute) If the plasma concentration (P_G) is sufficiently raised, the tubules though working to their full capacity will be unable to absorb all the glucose, and some ($U_G V$ per min) will reach the final urine Hence the maximal absorptive power of the tubules for glucose (T_{mG}) is the difference between the amount presented and the amount ultimately excreted—*i e* (C_{In} $P_G - U_GV$)

Derived Ratios—Measurements of the glomerular filtration rate, the effective renal plasma flow and the tubular capacity for reabsorption or excretion provide the framework for elucidating the mechanism by which other substances are excreted or for investigating abnormalities of renal function It must be realised, however, that these standards of reference are to some extent interdependent (apart from any mutual interference of the test substances which may introduce errors of measurement) Thus the inulin clearance may be subnormal because of some inherent defect in the glomeruli or because of some failure in the supply of plasma to them , these could be differentiated only by taking into account the renal plasma flow The ratio glomerular filtration rate (C_{In}) effective renal plasma flow (C_D), which is usually termed the *filtration fraction* would be normal if the blood supply were at fault but low if the glomeruli themselves were functionally defective

Similarly the ratio between the effective renal plasma flow and the maximum tubular excretory capacity (*i e* C_D/T_{mD}) may be interpreted as expressing the volume of plasma which may be supposed to be cleared of the test substance per unit of functioning tubular tissue A fall in this ratio may be interpreted as indicating relative ischæmia

A measure of the tubular efficiency in relation to the rate at which glomerular filtrate is supplied to them is given by the ratio between the glomerular filtration rate and the maximum tubular excretory capacity (*i e* $C_{In}T_{mD}$) , a high value would indicate tubular involvement (whether inherent or due to some aberration of supply to the tubules not affecting the glomeruli) more clearly than would a low T_{mD} alone

More complex formulæ based on the filtration rate, the mean arterial blood pressure, the renal blood flow, the plasma protein concentration and the renal venous pressure have been claimed to permit separate estimation of the afferent and efferent arteriolar resistance to the renal blood flow

Normal values for these functions and measurements are given in Table I

CLEARANCE TESTS IN CLINICAL MEDICINE

The clearance tests which have just been described are, it must be admitted, far too elaborate for everyday routine use when the only information desired is an answer to the question "is there kidney disease or is there not?", for that purpose much simpler procedures, amongst which must be numbered the Van Slyke urea clearance test, suffice Nevertheless their value is by no means confined to the elucidation of problems in pure renal physiology As research weapons, they have yielded information of the utmost value to the clinician in disentangling the abnormalities which make up the various diseases he has to diagnose and treat Every renal dysfunction must consist essentially of an imbalance of glomerular and tubular activities either intrinsically or through the associated extra-renal factors, and the real nature of such an imbalance can only be understood by a study of the discrete parts of the renal mechanism, that is, by renal clearance tests

TABLE I

Normal figures for Plasma Clearance and Derived Ratios in Man (adult males) The clearances for adult females are somewhat lower, but the ratios are the same These figures, from Smith's book are from his own laboratory, using the constant infusion method and are corrected to 1 73 sq m body surface (the conventional size correction) and 98 5° F rectal temperature

	Mean	Standard Deviation	Units
C_{In}	131 0	21 5	c c /min
C_D	697 0	136 0	
C_{PAH}	654 0	163 0	
T_{mD}	51 8	8 73	mg /min
T_{mPAH}	79 8	16 7	
$C_{In}/C_D \times 100$	19 2	3 5	
C_D/T_{mD}	14 0	2 16	
C_{In}/T_{mD}	2 63	0 344	

Time permits of no more than one example illustrating the clinical value of clearance studies, though many more could be given—the problems of essential hypertension, of the abnormalities comprising the " lower nephron syndrome," and of salt balance in chronic nephritis, to mention only three of considerable interest and importance Let us, however, contrast the typical findings in acute glomerulonephritis and in pyelonephritis, both possibly of bacterial origin (although different organisms, acting in different ways, are incriminated) but the one with the glomeruli primarily affected, whilst in the other tubular degeneration occurs first

In acute glomerulonephritis the inulin clearance is, of course, reduced, for it measures at least approximately the glomerular filtration rate The effective renal plasma flow, as measured by diodone clearance may also be reduced to a variable extent but the filtration fraction is markedly low (in spite of the hypertension) indicating the existence of loss of functional activity by the glomeruli themselves The T_{mD} is also low as a rule, and may be very low in a severe acute case or in the terminal stages of a chronic glomerulonephritis Nevertheless, the ratio C_{I_n} T_{mD} is well below the normal level, further indicating that the glomerular filter bed is especially affected Indeed, the residual functioning tubular tissue is capable of showing at least the normal excretory activity, for the ratio C_D T_{mD} is usually normal or even high With tubular activity maintained at a level closer to the normal than is the glomerular filtration rate, there is relatively little interference with the acidification of the urine (largely a function of the distal tubule) and therefore little tendency to acidosis On the other hand, the reduction in the amount of filtrate presented to the relatively active tubules per minute results in excessive reabsorption of sodium and chloride with, therefore, a tendency to œdema, whilst excessive reabsorption of urea combined with the diminished filtration may be an important factor in the elevation of the blood urea Similarly inefficient filtration accounts for the decreased potassium excretion and the high plasma potassium levels so frequently found in severe acute glomerulonephritis

The impression one gets is of a slow trickle of glomerular filtrate through relatively active tubules which therefore produce exaggerated modification of the filtrate

The picture is quite different in pyelonephritis with its easily-produced acidosis, its dehydration, its absence of hypertension and œdema Here the fault lies primarily with the tubules, and although the glomerular filtration rate, as indicated by inulin clearance, is somewhat below the normal, the effective renal plasma flow (C_D) is proportionately reduced so that the filtration fraction is normal This, especially in the absence of hypertension which might conceivably have partially compensated for glomerular failure, shows the fault in filtration to be extra-renal , probably the dehydration is a causative factor The tubular excretory capacity, measured by T_{mD} or T_{mPAH}, is very low, so that the ratio C_{In} T_{mD} is abnormally high In other words, the tubules are incapable of dealing adequately with even the reduced volume of glomerular filtrate which is supplied to them As one consequence of this failure, the urine is improperly acidified, fixed base is inadequately conserved, and acidosis occurs very easily The failure to conserve sodium means the excessive excretion of this ion with its attendant anions (mainly chloride), and therefore a tendency to salt depletion and secondary dehydration It is possible that the tubular damage may affect even the passive reabsorption of urea, for the urea clearance in relation to the glomerular filtration rate is occasionally high, and, in the earlier stages or less severe cases the blood urea rarely rises much above the normal level As the disease progresses, of course, glomerular degeneration occurs, filtration diminishes and, when the inulin clearance has eventually fallen to below a quarter of the normal, the symptoms of uræmia may begin to appear

The typical picture is of a relatively rapid and copious stream of glomerular filtrate supplied to badly damaged tubules which are quite unable to carry out the normal amount of modification by reabsorption and excretion

LIMITATIONS OF RENAL CLEARANCE TESTS

Enough has been said to demonstrate the value, for an understanding of renal disease, of the detailed examination of discrete renal functions which is permitted by clearance tests Even a cursory examination of any section of the vast literature which has, in no more than twenty years, been devoted to discussion of these tests, shows that their limitations are serious Many things conspire to make the interpretation of the measurements a matter, at times, of very considerable difficulty and even doubt In part, the complexity of the renal functions and of the impact of many extra-renal phenomena upon them, accounts for this But in addition there is the question of whether the standards of reference which purport to provide the means of measuring the individual parts of the excretory mechanism are sufficiently accurate under all circumstances Moreover the technical difficulties of the measurements themselves make it difficult to undertake (or to subject the patients to) the frequent observations which would be desirable in so many cases

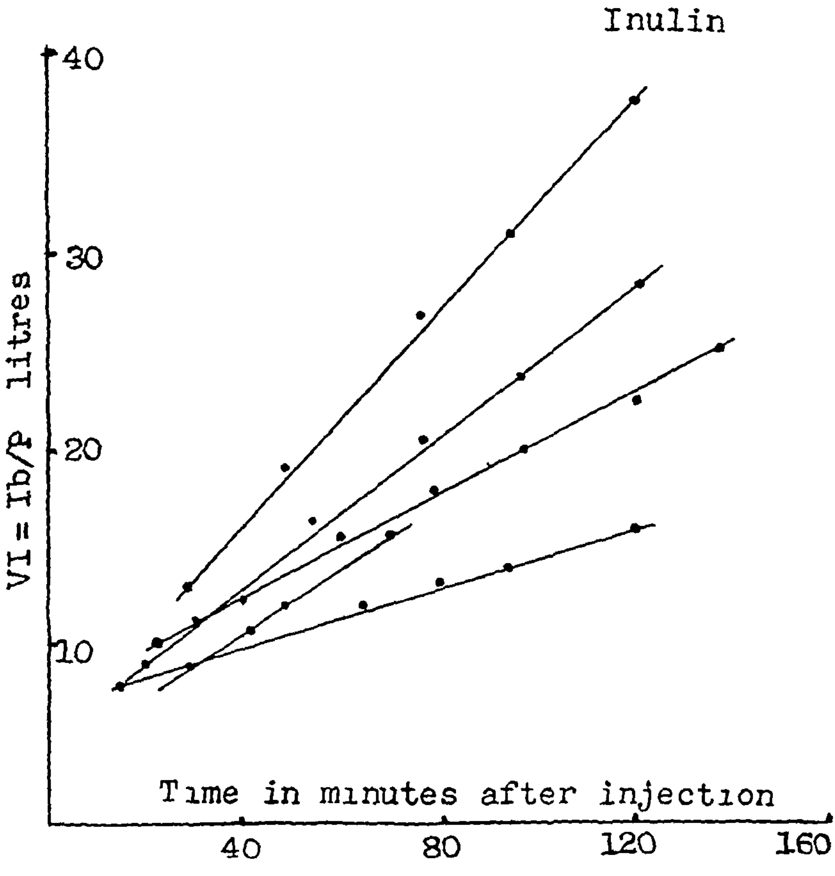

FIG 1*a* —The changing value of the expression —

$$\frac{\text{Amount of test substance remaining in the body (X}b\text{)}}{\text{Plasma concentration of test substance (P)}}$$

in five subjects after a single intravenous injection of inulin

Technique —On the technical side, many attempts have been made to avoid the necessity of giving a constant intravenous infusion of the test substance throughout the period of measurement, and of collecting urine carefully timed and accurately measured over short periods of time, (a necessity which demands catheterisation) The very number of these attempts demonstrates at once the potential value and the difficulty of clearance tests There are reasons for thinking that the constant infusion method is capable of giving the most accurate results over the widest range of circumstances but where, as is often the case, the clearance is not rapidly changing and the water distribution in the body is reasonably constant so that the time of measurement can safely be increased, my collaborators and I believe that a simpler technique can be satisfactory Even the constant infusion method is imperfect in the respects mentioned for it demands three successive " clearance periods " of ten minutes each, and the water distribution may be modified by the considerable volume of fluid infused

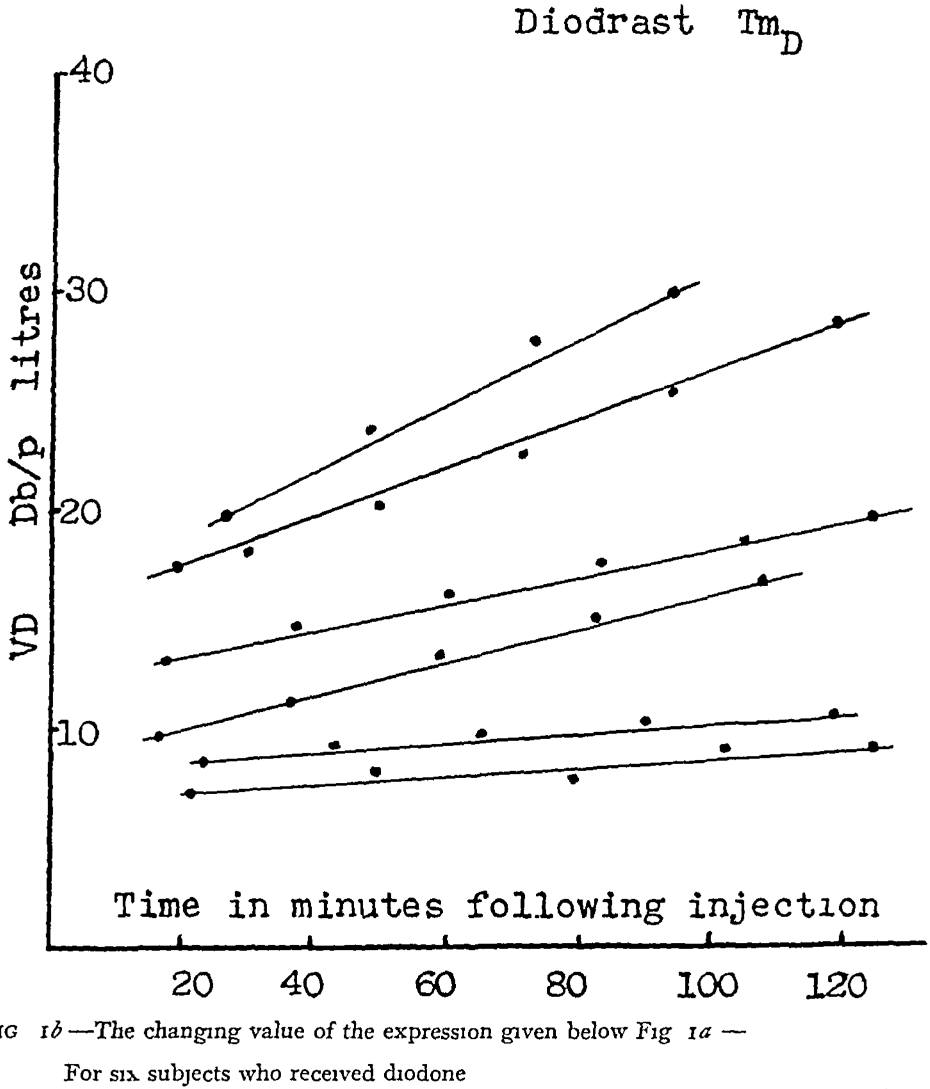

FIG 1*b*—The changing value of the expression given below Fig 1*a* —

For six subjects who received diodone

A maintained even distribution between plasma and extravascular fluid would give lines parallel to the base line in this and Fig 1*a*

The actual simplified procedure we have devised consists in giving, after a drink of water to promote urine flow, a single intravenous injection of the test substance—inulin, *diodone*, *p-amino*-hippuric acid, etc —of accurately measured amount At two suitable, carefully *noted times thereafter*, samples of venous blood are collected and the bladder is emptied, the times (usually 30 mins for the first collection, 60 or 100 mins for the second according to whether diodone or inulin is being employed) are such that catheterisation is usually unnecessary This simplification of technique depends upon recognition of the fact that with these substances and within these times, one cannot assume that equilibrium in the sense of an even distribution is *reached* and *maintained* between the plasma and extracellular fluid concentrations of the test substance If equilibrium were reached and *maintained thereafter, the amount of test substance remaining* in the body at any moment divided by the concentration in the plasma

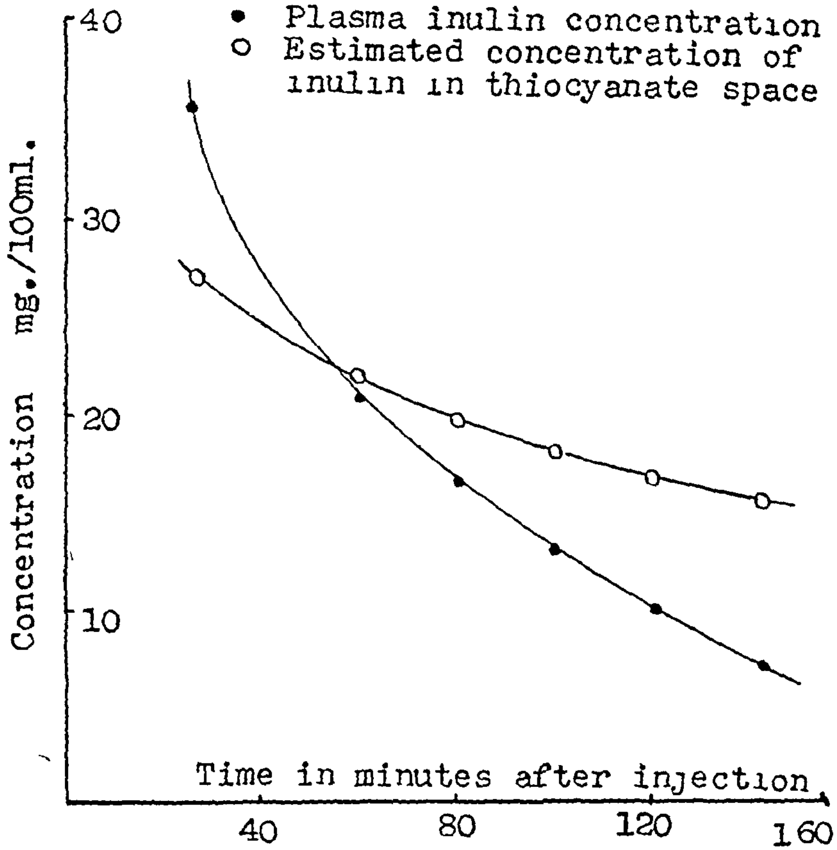

FIG 2—The changing concentration of inulin in plasma and extracellular fluid (calculated on the basis of thiocyanate space) after a single intravenous injection Only at one instant in time do the concentrations coincide This curve has the same significance as the lines in Fig 1 and is really another and perhaps more striking way of presenting the same data

at that same moment would be constant, in fact under the conditions considered, this is not the case as is shown for inulin and diodone in Figs 1 and 2 On this basis, assuming that (as Fig 1 shows) the change in the value of the expression —

$$\frac{\text{Amount of X in the body}}{\text{Plasma concentration of X}}$$

is regular (*i e* linear), it is possible to derive formulæ for the calculation of the clearances The derivation of these formulæ has been given fully elsewhere They are —

Inulin Clearance —

$$C_{In} = \left[\frac{b\,(\log (P_I)_1 - \log (P_I)_2)}{\log (V_I)_2 - \log (V_I)_1} - b\right]\left[\frac{10^4}{10^2 - PP}\right]$$

Diodone Clearance —

$$C_D = \left[\frac{q\,(\log (P_D)_1 - \log (P_D)_2)}{\log (V_D)_2 - \log (V_D)_1} - q\right]\left[\frac{10^4}{10^2 - PP}\right]$$

Maximum Tubular Capacity for Diodone —

$$T_{mD} = (C' + m)\ \frac{(P_D)_2(V_D)_2^x - (P_D)_1(V_D)_1^x}{(V_D)_1^x - (V_D)_2^x}$$

In these formulæ —

$(P_I)_1$, $(P_I)_2$, $(P_D)_1$, $(P_D)_2$ = Plasma concentration of substance in first or second sample

V_I or V_D = (Amount of substance injected—Amounted excreted)/Plasma concentration

$b = \frac{(V_I)_2 - (V_I)_1}{t_2 - t_1}$, q (or m) $= \frac{(V_D)_2 - (V_D)_1}{t_2 - t_1}$, $x = \frac{C' + m}{m}$

$C' = FWC_{In}$ where F = filterable fraction of diodone and
W = percentage water content of plasma = 100—PP

PP = plasma protein content

t_1 and t_2 = times of blood and urine collection (t_0 = time of injection)

Although they look complex their use is not really difficult, and involves much less expenditure of time and effort than does the manipulative and analytical work of the constant infusion technique That agreement between this and the standard methods is good is shown in Table II which also shows, however, that in the case of diodone clearance the simple method employing venous blood gives lower results than the standard, this is not a serious disadvantage though it demands the use of a different normal standard and it can be overcome by using arterial blood for the analysis With the development of suitable micro-methods, on which we are at present engaged, it may become possible to use capillary blood and so abolish the difference

Apart from the impossibility of noting rapid fluctuations in clearance by the single injection method there are other possible objections to its use—*e g* when the plasma concentration of the test substance is altering, there must be a time interval before the alteration is reflected in the urine and this interval may vary with the rapidity of the change However, under the specified conditions, agreement between the two methods is sufficiently good, and it becomes a matter of deciding the method to be employed for a given purpose according to the type of information required and the complexity of technique which is desirable or permissible But it is obvious that the technique of clearance measurements has not yet reached perfection

TABLE II

Typical examples showing agreement between clearances determined by constant infusion and those determined by single injection, but (necessarily) at a different time The correction applied to the C_D *figures is necessary, for comparison, to allow for the fact that venous blood was used in the single injection determinations , it is based on determinations of the arterio venous difference*

C_{In}		C_D		
Infusion	Single Injection	Infusion	Single Injuection Venous Blood	Single Injection+20 per cent (Correction for Arterio venous Difference)
132	130	650	500	600
105	103	540	431	517
86	74	446	363	435
52	56	277	248	297

Standards of Reference—The difficulty of deciding upon test substances which will behave so precisely as the theory of renal function demands that they can be relied upon to measure accurately the rate of glomerular filtration, the effective renal plasma flow, etc , is indicated by the long list of such substances which have been tried and found wanting For measurement of glomerular filtration rate inulin is now the most generally used substance, but there is evidence to suggest that it is by no means perfect Indeed one may wonder whether there exists in fact any substance which is wholly filtered by the glomeruli without alteration in concentration and is absolutely unaffected by tubular activity If inulin did behave in this way, the amount excreted per minute (UV) would be a constant multiple of the plasma concentration (P), so that if UV were determined for various values of P, and UV were plotted graphically against P the result would be a straight line passing through the origin However, in 15 cases which we examined, using both the single injection and the constant infusion method, the straight line connecting the points when UV was plotted against P did not pass through the origin The relation between UV and P was given not by the equation UV = KP but by UV = KP—a (Fig 3) This afforded good evidence for believing that inulin is in fact partly reabsorbed by the tubules and that in normal people the true glomerular filtration rate is some 15 per cent

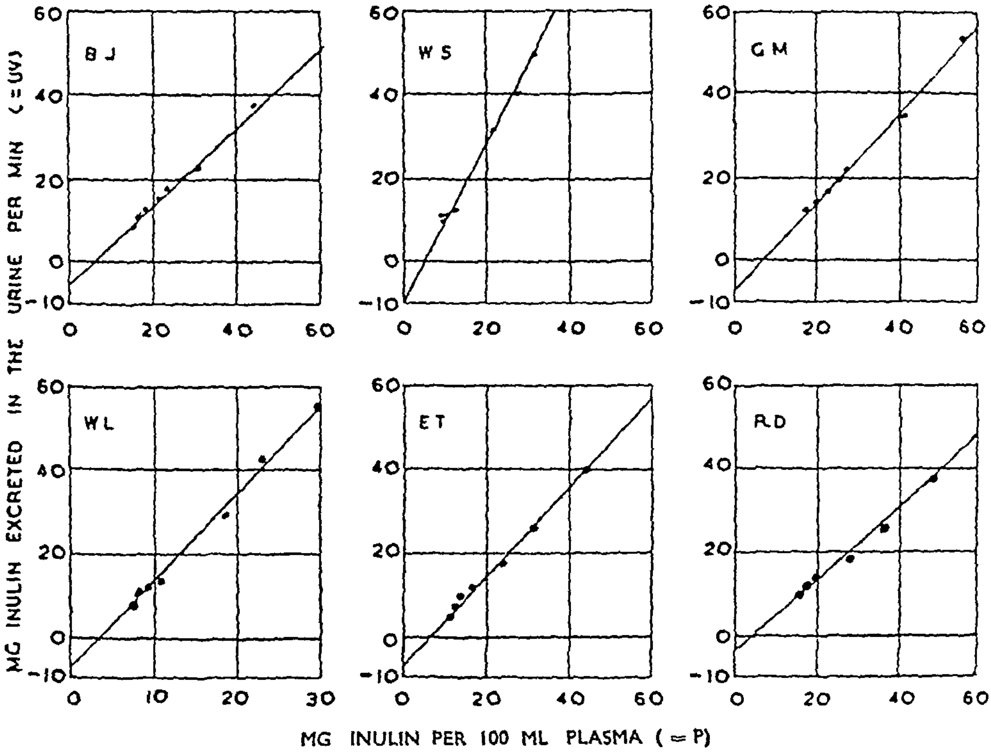

FIG 3—The rate of inulin excretion (UV) plotted against the plasma inulin concentration (P) If $\frac{UV}{P}$ were constant for all values of P, the lines would pass through the origin

higher than is indicated by the inulin clearance It may well be that the discrepancy is greater when the kidneys are diseased, for we have found, in a few severe cases of chronic nephritis that the inulin clearance was lower than the urea clearance but that in the one case where the experiment was tried, the inulin clearance was markedly increased when the urine flow was forced to the maximum of which the damaged kidneys were capable A similar abnormality of the C_{In}/C_{UREA} ratio has been reported by Raaschou in a few cases of pyelonephritis, and although a different explanation was advanced, there is evidently some dubiety about the validity of the claim that inulin provides a reliable and accurate measure of the glomerular filtration rate For many purposes the approximation is doubtless sufficiently close, but the fact that the measurement is merely an approximation undoubtedly limits the usefulness of clearance tests by introducing some uncertainty into their quantitative interpretation

There is, at least in the presence of severe renal damage, a similar doubt about the reliability of diodone and *p*-amino-hippuric acid as test substances for the measurement of effective renal plasma flow

If they are really completely excreted from the plasma during one passage through the nephrons, the "extraction ratio" (the ratio of the difference between the concentrations in arterial and renal venous plasma to the arterial concentration) should be 1 0 In health the extraction ratio does approach closely to 1 0 but in nephritis it may be as low as 0 5 or even less This may mean that with destruction of the renal parenchyma more and more blood reaches the renal side from the arterial without passing over functioning tubular tissue, but this suggestion cannot be substantiated and the element of uncertainty persists

Interference—For a strict comparison of clearances in a given individual, measurements ought to be simultaneous This is especially true when the conditions under which the kidneys function are subject to rapid change Yet the ideal is frequently unattainable, for one test substance may interfere with the excretion of another This is of course particularly true of measurements of tubular activity Tubular excretion appears to involve only two transport systems with a factor common to both, hence loading the tubules with a substance X to measure T_{mx} depresses the excretion of all substances in one or other of two groups Even tubular reabsorption and tubular excretion may be mutually competitive for it has been found repeatedly that the simultaneous measurement of T_mPAH and T_mG gives low values for both (but—a further indication of the difficulties involved—this may be due to interference in the methods of chemical analysis)

Interference may be produced by extra-renal factors and although some of the curious results obtained when clearances are measured during hormone imbalance may be real in the sense that the imbalance specifically affects discrete parts of the renal mechanism, they may merely be due to extra-renal disturbances Thus in one case with apparently normal renal function recently studied in my laboratory, the continued administration of A C T H resulted, on the fifth day, in a marked increase in the inulin clearance to a level far above the normal, whilst there was no accompanying increase in the urea clearance or the diodone clearance The phenomenon may possibly be due to dilatation of the afferent arterioles with constriction of the efferent arterioles At least it illustrates the difficulties in interpreting in such circumstances the results of clearance tests and therefore emphasises their limitations Yet it also illustrates their value, for the demonstrated changes in renal activity, however produced, must be largely responsible for the alterations in the excretion of electrolytes and other substances which are so marked a feature of hormonal abnormalities

Finally, it should again be emphasised that interpretation of renal clearances is based on the accepted theory of renal mechanism There is little doubt that this theory is correct in broad outline, but it may (and probably will) be modified in detail as knowledge increases In particular it seems doubtful whether the present view that one substance is reabsorbed and not excreted by tubular activity whilst another is excreted and not reabsorbed will survive more complete examination of the transport systems Also, it may become necessary to take more cognisance than has hitherto been done of the effects of the Donnan equilibrium and perhaps other physico-chemical factors in altering the composition of the plasma during glomerular filtration

CONCLUSION

I am very conscious that this brief outline of the nature, uses, and limitations of renal clearance tests may by the omission of detail and of full discussion of many controversial matters, have failed to give a true picture I hope, however, that I have succeeded in demonstrating that these tests provide a potent weapon which has already given a greatly increased undertanding not only of renal physiology pure and simple, but of the varied derangements of renal function And it should be reiterated that, with all their faults and limitations, we owe to them much of our knowledge of many other abnormalities besides those primarily due to renal disease, such as the serious disturbances of salt and water balance which occur in Addison's disease, congestive heart failure, Cushing's syndrome, and the like Though not—as yet, at least—ordinary everyday " routine " tests they are steadily increasing our insight into the aberrations which make up many disease processes and they are therefore of the utmost value to the clinician who must appreciate, implicitly or explicitly, the mechanism involved in the disease he hopes to treat by a rational therapy

REFERENCES

A full bibliography for this lecture would be quite out of place, even if it were possible The book by Homer Smith lists 2500 references Two of the figures and some of the statements in the text are drawn from published accounts of work done in the author's laboratory The references to these are —

ROBSON, J S , FERGUSON, M H , OLBRICH, O , and STEWART, C P (1949), *Quart Journ Exp Physiol*, 35, 111, 173

FERGUSON, M H , OLBRICH, O , ROBSON, J S , and STEWART, C P (1950), *Quart Journ Exp Physiol*, 35, 251

OLBRICH, O , FERGUSON, M H , ROBSON, J S , and STEWART, C P (1950), *Lancet*, Nov 18th, 565

THE PATHOLOGY OF FŒTAL AND NEONATAL ASPHYXIA

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SIR JOSEPH BARCROFT, to whose work on fœtal respiration we owe so much that is known of this subject, defined fœtal asphyxia as " that combination of oxygen lack and carbon dioxide excess wrought by occlusion of the umbilical cord " (Barcroft and Barron, 1937-38) It is primarily a state of oxygen lack Other phenomena that may accompany this state, such as disturbance of carbon dioxide content, the production of organic acids and the development of acidosis, are secondary to oxygen lack and dependent upon it Many people, therefore, prefer the term " anoxia " to " asphyxia," though the purists object that the condition referred to is rarely, if ever, literally anoxia, and prefer the less familiar term " hypoxia " I am not greatly concerned about what term is used, so long as it is understood that the subject I am attempting to discuss is the causes and consequences of dangerous degrees of oxygen lack in the fœtus and newly born child, in so far as these can be studied by the methods of the morphological pathologist

It is recognised that the tolerance of the fœtus and newborn to anoxia is high compared with that of older subjects The ability to survive anoxia depends finally on the ability of the brain to survive, as this is, of all organs, the most vulnerable to anoxia It is believed that the effect of anoxia on the brain, including the medullary centres, is purely depressant, and although impulses reaching the brain from the chemoreceptors are increased by anoxia, these are of no avail when the medulla is so depressed that it is unable to respond Anoxic deaths are due to anoxic depression and death of nerve cells in the brain The immature brain of the newly born has a lower oxygen requirement, and consequently a higher tolerance of anoxia than the fully developed brain of the older subject Other factors in the higher anoxic tolerance of the fœtus are an ability to utilise more completely such oxygen as is available, and a capacity for anærobic respiration, by means of glycolysis, which makes survival possible for short periods under conditions of anoxia that would inevitably be fatal to an older subject

The causes of fœtal anoxia are well known briefly they are these Interference with the circulation of blood through the placenta and cord, by prolapse, knots or twists of the cord, or by premature separation of the placenta , placental insufficiency due to infarction, disease or postmaturity , prolonged pressure on the fœtal head during labour, causing

A Honyman Gillespie Lecture delivered on 25th October 1951 anoxia of the brain by impeding venous return, and some anoxic conditions of the mother, such as anæmia, cardiac disease and anæsthesia The risk to the fœtus of asphyxiant anæsthetics is now recognised, and it seems that respiratory depression resulting from narcotic drugs is less dangerous than that due to anoxia

The contribution that can be made to knowledge of this subject by the morphological pathologist is limited The solution of most of the fundamental problems must be sought in those alterations of function and reactivity that lie for the most part beyond the reach of the histologist's methods But the contribution that pathology has already made is not negligible, nor has the limit of what it may contribute yet been reached This contribution is to reveal the magnitude of the problem in terms of loss of infant life, and to attempt to present morphological facts with which morbid changes of function can be correlated

Asphyxia as a Cause of Fœtal and Neonatal Deaths—It is not unfair to claim that the present widespread interest in and concern about the results of fœtal and neonatal asphyxia took origin in the revelations made by pathologists as a result of study of large numbers of autopsies in cases of stillbirth and early neonatal death Such studies have invariably indicated a high prevalence of asphyxia in these fatal cases In fact, nearly all intra-uterine, intra-natal and early neonatal deaths are anoxic deaths, so the problem of anoxia enters into nearly every problem of what is now being called "perinatal mortality" If one excludes cases in which anoxia is secondary to some other major cause of death (such as traumatic intracranial hæmorrhage) the number of deaths primarily attributable to asphyxia is still formidable Among stillbirths it amounts to at least two-thirds of all cases Among the liveborn, published work gives percentages varying from about 12 to 40 per cent of deaths during the first month of life, nearly all occurring within the first three or four days If cases are included in which death is caused by certain lethal lesions (such as some forms of hæmorrhage) that are in all probability dependent, or partly dependent on anoxia, the percentage of neonatal deaths that can be attributed to anoxia is certainly not below the higher figure quoted, and probably exceeds one-half of all such deaths And with the better control of infection and of trauma, which in recent years has eliminated so many neonatal deaths, the percentage due to asphyxia is now higher than even a few years ago

The classical pathological appearance of death from asphyxia are seen to greatest advantage in dead-born fœtuses at, near, or after term, in which the degree of anoxia has been very severe In these cases the typical picture is one that is common to acute asphyxia at any age, with all the features very well developed, and with, in addition, certain other features that are peculiar to fœtal asphyxia The common features are universal venous engorgement, dark, fluid blood, delayed clotting, petechial hæmorrhages under the thoracic serous membranes, in the thymus gland and elsewhere, and a dilated heart The features peculiar to fœtal asphyxia are those produced by inhalation of contents of the amniotic sac

Among physiologists who have studied fœtal respiratory function it is generally agreed that the fœtus, from an early stage of development, is capable of making movements resembling those of breathing This was proved by Barcroft in sheep fœtuses (Barcroft and Barron, 1937) and has been confirmed by others in various animals , and there is good evidence that it is true also of the human fœtus Barcroft (1934, 1947) described three types of respiratory movements, each representing a level of control by nervous centres These he demonstrated by the study of fœtuses at different stages of development, during which the effects of the three centres are added from below upward , and also by the study of the effects of cyanide poisoning in adult animals, by which the control of the three centres is progressively removed from above downward As cyanide acts by preventing oxygenation of tissues, the results of these experiments are applicable to naturally occurring conditions of anoxia When only the first developed, or lowest, centre is in control, the type of respiratory movement made is the "primitive gasp," an isolated movement of considerable depth When the second level of control operates, the movements are of the type described by Barcroft as the "single prolonged inspiration" or "apneusis" , and only when the third and highest centre takes control is regular, rhythmic respiration of normal type—"pneumotaxis"—established All these types of respiratory movements can be performed by the fœtus, and they can be elicited by various mechanical stimuli and as a response to anoxia Thus far there is fairly general agreement Opinions differ as to whether any of these movements occur *in utero* under normal conditions, and as to whether, if they do occur at all, the movements of pneumotaxis (which alone can be considered normal after early fœtal life) are of sufficient amplitude to draw into the lungs the amniotic fluid that forms the intra-uterine environment of the fœtus Some answer both these questions in the affirmative, others in the negative, believing that the fœtus is normally apnœic, and that only the deeper movements released by anoxia are capable of causing aspiration of amniotic fluid

The pathologist, attempting to interpret his observations, is placed in a quandary by this disagreement among the physiologists, and is thrown back on his own observations, which, in my experience, are these Amniotic fluid is not difficult to recognise in the lungs of a fœtus The fluid itself has a low protein content and cannot be distinguished in histological sections from the fluid of transudates But it contains in suspension solid debris that is readily identified cornified squames and fine hairs from the skin of the fœtus, fragments of epithelium from the amnion, and sometimes fibrin, blood and pus cells The cornified squames especially, when present numerously in the lungs of a fœtus or newborn infant, prove that amniotic fluid has been inhaled in quantity It has been my experience that those fœtuses in which evidence is found of aspiration of large amounts of amniotic fluid are those in which the general evidence of asphyxia is most clear, and that those in which some other adequate cause of death is present and the general signs of asphyxia are slight or absent, are those in which evidence of aspiration is least likely to be found Further, it seems certain that solid amniotic débris in the fine bronchi and alveoli cannot fail to obstruct air entry to some extent and thus to be injurious to the infant after birth It has been argued (Snyder and Rosenfeld, 1937) that this solid material is present only when the amniotic fluid is abnormal, in that it contains an abnormal amount of débris, as when a severely asphyxiated fœtus has passed meconium and this is aspirated along with the amniotic fluid This accident does certainly increase very greatly the amount of débris that may enter the lungs (Fig 1), but I have found that amniotic fluid almost always contains enough solid débris to make it certain that much must be inhaled along with any fluid that enters the lungs If continuous inhalation of amniotic fluid is really a normal occurrence, it would seem that all fœtal lungs must contain great quantities of this solid debris. This is not so I find myself, therefore, in full agreement with Windle's opinion (1950) that inhalation of liquor amnii is not a physiological occurrence but happens only under conditions of anoxia in which the fœtus makes abnormal respiratory movements of great amplitude I therefore include the finding of amniotic débris in quantity in the lungs among the most important and reliable pathological signs of fœtal asphyxia

Thus far we have been considering the asphyxiated fœtus that is born dead, in which intra-uterine anoxia has reached so severe a degree that the vital centres are paralysed and the functions of respiration and circulation cease before birth We come now to consider asphyxia as a cause of the deaths of live-born infants in the early days of independent life These may be considered in two groups (1) Infants who are asphyxiated at birth and fail to establish and maintain a satisfactory respiratory function after birth, and (2) infants who have not obviously suffered from anoxia before or during birth and who may appear to be in reasonably good condition at birth, but who become anoxic subsequently, having failed to maintain oxygenation of their blood, and die usually within three days after birth

Cases in the first group (infants born asphyxiated) represent merely another aspect of the problem of the anoxic stillbirth The causes are the same, the pathological effects are of the same kind, but the vital functions are still possible, even though impaired In these cases the fact of birth and the demand that the infant must now supply himself with the oxygen that he has hitherto received from his mother, introduce a new factor If the medulla is so far depressed that it can no longer respond to the stimuli that normally produce the first breath and cause breathing to continue, resuscitation will fail and the child will speedily die If, however, breathing is attempted, any amniotic fluid

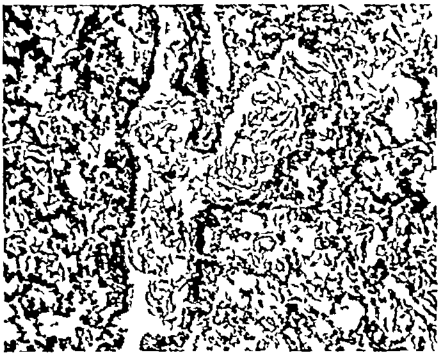

FIG 1—Lung of asphyxiated fœtus Bronchus and alveoli filled with debris from amniotic fluid contaminated with meconium H & E ×100

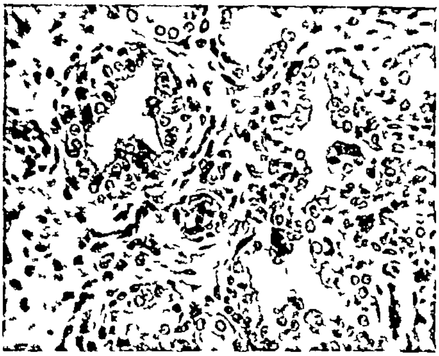

FIG 2—Lung of fœtus of 850 gms Air spaces lined by cubical cells and separated by thick septa of primitive mesenchyme H & E ×425

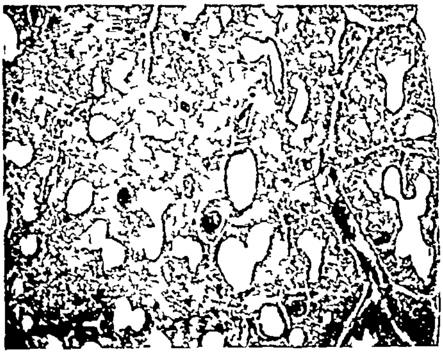

FIG 3—Lung of premature infant of 940 gms who survived one day Overdistension of bronchioles with complete atelectasis of alveoli H & E ×25

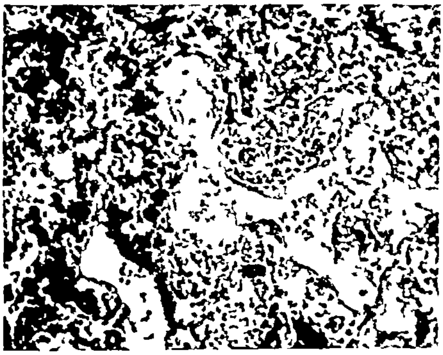

FIG 4—Lung of premature infant of 1800 gms who survived two days Hyaline membrane lining alveolar ducts Early inflammatory reaction H & E ×160

or debris that may be in the lungs, which hitherto has been harmless, now becomes a handicap to respiration and a menace to life, impeding aeration of the lungs and causing a progressively worsening anoxia In severe cases of this type survival is usually short, but in less severe cases recovery is possible, or the child may die after some hours or days of precarious survival Among such infants who ultimately succumb, as among the second group of infants who become anoxic after birth and die, there is a large preponderance of prematures It would seem that the full-time infant, even though seriously anoxic at birth, if he is capable of beginning to breathe, usually contrives to get enough oxygen to allow him to break out of the anoxic vicious circle and survive But the premature has far more difficulty both in establishing air breathing and in maintaining oxygenation, and is all too apt to be caught up in that vicious circle in which the more he is in need of oxygen the less he is able to get it into his blood Neonatal anoxia is thus to a very large extent a problem of prematurity, and so it may be appropriate to consider some of the handicaps under which the premature baby is placed in his efforts to attain and maintain adequate oxygenation

The first essential for adequate oxygenation is the possession of respiratory centres capable of performing their necessary function It is often assumed that much of the respiratory difficulties of the premature derives from inefficiency of immature respiratory centres There is some evidence from physiological studies that the respiratory centres of premature infants (including the chemoreceptors) are capable of prompt and vigorous response to their appropriate stimuli, but that their adaptability is less and that there may be difficulty in maintaining an adequate response to oxygen lack over any considerable period There are, also, abnormalities of respiration that are common in the premature, such as periodic breathing with periods of apnœa Whether any of these peculiarities should be attributed to immaturity of the centres or to some other factors is not known

The second essential for adequate oxygenation is the possession of a respiratory apparatus properly adapted to procure ventilation of the lungs and oxygenation of the blood in them In this respect the premature is demonstrably ill equipped The chest wall is soft and flexible, the respiratory muscles are poorly developed and weak Respiration is almost entirely abdominal and may produce very little movement of the thoracic wall This is an obvious handicap to the child in the business of expanding the lungs Further, the lungs themselves are poorly adapted to the function that has been untimely thrust upon them At term, the development of the lungs is, for practical purposes, complete and their structure resembles in all essentials that of adult lungs The distal air spaces, or alveoli, are perfectly developed, their walls are thin, fully vascularised, and equipped with their proper content of elastic fibres Such lining cells as the alveoli still possess are flattened, and they form a discontinuous layer, through the gaps in which the capillaries in the alveolar walls protrude, to come into direct contact with the air in two contiguous alveoli, *thus facilitating to the greatest* possible extent the exchange of gases between the inspired air and the blood It is, however, only near normal term that the fœtal lungs attain to this degree of structural perfection In the early stage of its development the lung is formed by the budding and branching of the primitive bronchi into a mass of primitive mesenchyme These, by progressive branching, form primitive ducts and canals, and only fairly late in development are true alveoli formed At this incomplete stage of development, which still obtains when the fœtus reaches what is regarded as viable age, and for some time thereafter, the most distal existing air spaces still retain a continuous lining of cubical epithelium, and an appreciable amount of the primitive mesenchyme persists in the septa between them (Fig 2) The capillaries in these septa are thus separated from the lumen of the air space by a certain thickness of this tissue and by a layer of thick cubical epithelial cells, which still remains continuous after expansion with air And there is, at this stage, little or no elastic tissue in these septa

It may be said, therefore, that, compared with the full-term infant, the premature has lungs that are more resistant to expansion, owing to the excessive thickness of the septa, less resilient, owing to lack of elastic tissue, and less well adapted for the exchange of gases, owing to the thickness of tissue between the capillaries and the air It is reasonable to correlate these anatomical observations with the facts that a premature infant takes much longer than a full-term infant to expand its lungs completely, even when breathing is normal, and has more difficulty with the transfer of oxygen from the lungs to the blood

Atelectasis in the premature may be a very important factor causing or aggravating neonatal anoxia Pathologists are familiar with the picture of a premature baby who has lived for twenty-four hours or more, and whose lungs show at autopsy no visible aeration, sink heavily in water, and, on microscopical examination, show that no air has penetrated beyond the alveolar ducts, and even only to a few of those, so that one can only marvel that life was sustained for so long These extreme cases are most usual when the child has suffered from anoxic depression at birth, or where some obstruction to air entry (*e g* by liquor amnii, or vernix, or hyaline membrane) exists in the respiratory passages or lungs But even when the efforts to breathe are vigorous there may result a condition in which acute overdistension of the bronchioles is accompanied by complete atelectasis of the air spaces distal to them (Fig 3) Such a misfortune of mal-expansion is most likely when some cause of obstruction exists , or may easily be produced by ill-advised attempts at artificial inflation , but can result apparently from the infant's own efforts with lungs poorly adapted, by reason of immaturity, to their respiratory function

Another common pathological condition in the lungs of the newly born that has a close bearing on neonatal anoxia is the pulmonary hyaline membrane (Fig 4) It is found in about one-half of all premature infants who die in the first two weeks after birth, and in a smaller percentage (from 12 to 25 per cent according to different observers) of full-term neonatal deaths Most cases occur in infants that die between one hour and four days after birth It does not occur in the stillborn For long it was known as "vernix membrane," the name given to it by the Boston school led by Farber (Farber and Sweet, 1931) who believed that it was composed of vernix caseosa inhaled by the fœtus with liquor amnii This theory was generally, and perhaps too uncritically, accepted, and it is surprising that it held the field for so long , for if vernix, collected from the skin of a fœtus or from the liquor amnii, is processed in the same way as an ordinary paraffin section, it appears, when its fatty matrix has been removed, to be composed entirely of cornified cells having exactly the same appearance as those that form deposits in the lungs of asphyxiated fœtuses, and bearing absolutely no resemblance to the hyaline membrane During the past two years the vernix theory has fallen into disfavour and has been superseded by theories in surprising variety It has been suggested that the membrane is caused by injury of unspecified nature by an unspecified noxious agent, to the epithelial lining of the respiratory tract (Miller and Hamilton, 1949) , that it is a product of lysis of the epithelial lining of the immature lung on expansion at birth , that it is a result of aspiration of acid gastric juice (Ahvenainen, 1950) , that it is caused by administration of oxygen (Bruns and Shields, 1951) , that it results from disturbed nervous impulses through the vagus (Miller, Behrle and Gibson, 1951) Quite recently, the Boston school (Blystad, Landing and Smith, 1951) has produced a revised version of the amniotic aspiration theory of Farber, suggesting that the membrane is formed from the protein content of amniotic fluid, concentrated after a period of air breathing and deposited in membrane form This theory, if proved, would restore this condition to its place among the effects of fœtal anoxia None of the new theories can be accepted until further study and experimental investigation have been carried out , and until the nature and origin of the membrane are certainly known it must remain in doubt whether or not anoxia is responsible for its production Nor is it surely known that it is a cause of neonatal anoxia, but histological study strongly suggests that it is The presence of hyaline membrane is almost invariably associated with severe atelectasis The membrane usually forms in alveolar ducts, and it appears to block the entrances to the more distal air spaces, preventing their expansion or causing them to collapse Sometimes the affected ducts become greatly over-distended, and interstitial emphsema may result, the whole picture being indicative of obstruction to the passage of air Moreover, in those air spaces to which air penetrates, the presence of a thick layer of membrane interposed between the air and the blood in the capillaries must surely interfere seriously with the exchange of gases It is therefore reasonable to assume that the membrane is an additional handicap to respiration and a factor in producing or aggravating neonatal anoxia It is not known how often infants thus affected survive, but it may be that the much higher incidence of hyaline membrane in the premature at autopsy is in reality due to a much higher survival rate among the mature

The discussion of the pulmonary aspects of fœtal and neonatal asphyxia cannot be completed without reference to pneumonia The relation between fœtal asphyxia and those cases of pneumonia that occur before or soon after birth is very close In many cases the pneumonia is caused by aspiration of infected liquor amnii by an anoxic fœtus , and in other cases the water-logged and ill-ventilated lungs of the newly born with anoxic depression and atelectasis provide a favourable site for the development of a post-natal infection I have found that most of these anoxic infants who die on or after the third day have developed pneumonia These cases of pneumonia are appropriately termed " post-asphyxial " The pneumonia must be regarded as secondary to the asphyxia, but it often causes the death of an infant who might otherwise survive

Time will permit only brief reference to the relation of asphyxia to hæmorrhage, that other most important cause of fœtal and neonatal death Petechial hæmorrhages, as has been said, are among the recognised pathological signs of asphyxia, but there is some doubt about the role of asphyxia as a cause of major hæmorrhage That the two are often associated is known to every pathologist, and it seems certain that some of the effects of asphyxia must favour hæmorrhage the venous engorgement, the raised blood pressure, the delayed clotting of blood, the decreased capillary resistance There are many forms of fœtal and neonatal hæmorrhage in which it is by no means clear that direct trauma plays any part and it is more than likely that anoxia is, at the least, one of several factors that may be responsible As an example may be cited intraventricular cerebral hæmorrhage Although it is occasionally found in a stillborn fœtus and in a full-term liveborn child, the usual victim is a small premature who has lived one to three days or sometimes longer Often he has been anoxic at birth, though this is not invariably so according to the history The source of the intraventricular bleeding is usually a hæmorrhage from a vein under the ependyma, rupture of which releases free hæmorrhage into the cavity of the ventricle The hæmorrhage may thus occur in two stages, the first of which may well be related to anoxia in the same way as other petechial hæmorrhages, to which it is comparable In similar fashion, small venous hæmorrhages under the capsule of the liver may progress to form a large hæmatoma, and ultimately, through rupture of the capsule, may produce massive and rapidly fatal intraperitoneal hæmorrhage

It is evident, therefore, that many deaths may be attributed to infection, and many to hæmorrhage that ought properly to be laid to the account of asphyxia, which will then be revealed in its true role as the principal single cause of fœtal and neonatal death

REFERENCES

AHVENAINEN, E K (1950), *Ann Med Int Fenniæ*, 39, 215
BARCROFT, J (1934), *Features in the Architecture of Physiological Function*, Cambridge University Press
BARCROFT, J (1947), *Researches on Prenatal Life*, Springfield, Thomas
BARCROFT, J, and BARRON, D H (1937-38), *Journ Physiol*, 91, 329
BARCROFT, J, and BARRON, D H (1937), *Journ Physiol*, 88, 56
BLYSTAD, W, LANDING, B H, and SMITH, C S (1951), *Pediatrics*, 8, 5
BRUNS, P D, and SHIELDS, L V (1951), *Amer Journ Obst Gynec*, 61, 953
FARBER, S, and SWEET, L K (1931), *Amer Journ Dis Child*, 42, 1372
MILLER, H C, BEHRLE, F C, and GIBSON, D M (1951), *Pediatrics*, 7, 611
MILLER, H C, and HAMILTON, T R (1949), *Pediatrics*, 3, 735
SNYDER, F F, and ROSENFELD, M (1937), *Journ Amer Med Assoc*, 108, 1946
WINDLE, W E (1950), *Asphyxia Neonatorum*, Springfield, Thomas

THE ASSESSMENT OF INADEQUATE LACTATION

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For the diagnosis of inadequate lactation in women it is essential to know the signs and symptoms and tests which may be of value in the assessment of lactation Since these signs, symptoms and tests have rarely been correlated a series of observations have been made on cases of inadequate lactation occurring in the Simpson Memorial Maternity Pavilion, Edinburgh

SYMPTOMS AND SIGNS IN INADEQUATE LACTATION IN THE MOTHER

The clinical picture, prognosis and treatment of inadequate lactation in women depends on whether the condition is due to a fall in milk yield or to an increase in the infant's demands which exceeds the mother's maximum yield The clinical picture due to a reduction in milk yield is most often seen in women between the second and sixth week of lactation After the sixth week few mothers experience this type of lactational disorder unless they wilfully stop suckling their infants at three or four hourly intervals throughout the day Various symptoms and signs occur in such a condition but they are not constant and few are pathognomic of inadequate lactation For instance the mother finds her breasts do not feel tense or firm by the time a feed is due, her milk stops leaking from the nipples and she no longer experiences the " draught " She may also notice that her breasts are not appreciably softer after feeding her infant than they were before the feed In the initial stage of failing lactation and when the deficiency is not marked symptoms and signs are minimal and may possibly be absent When they first appear they are more likely to be detected during the latter half of the day than in the morning If such women are observed for a week or so such signs and symptoms become more apparent in the majority of cases because of progressive diminution in milk yield As a rule such women are forced to give their infants artificial feeds within a few weeks of the onset of such symptoms

The symptoms and signs of the second type of inadequate lactation occur after the neonatal period and are due to the mother's milk yield failing to increase sufficiently to meet her infant's growing demands They usually arise in the third to sixth month of lactation but are occasionally encountered before that stage of lactation These women are not conscious of any alteration in their ability to lactate On the contrary they are convinced they have plenty of milk for their infants because their breasts fill well and the milk may even leak from the nipples between the feeds or while the infant is being suckled Thus inadequate lactation is not suspected until the infant is weighed and its weight gain is found to be unsatisfactory A provisional diagnosis of inadequate lactation is made and later is confirmed by the results of test-weighing Provided the infant is given suitable complementary feeds he will progress satisfactorily, premature weaning being unnecessary in such cases

SYMPTOMS AND SIGNS OF THE UNDERFED INFANT

While the majority of underfed infants are readily diagnosed by the alteration in their behaviour and stools and by their unsatisfactory weight gain, it is not so generally known that the milk from mothers with a scanty *milk yield acts as a gastro-intestinal irritant in* some cases (Still, 1927) Confirmation of this statement was obtained when 24 underfed infants were observed for periods ranging from one to sixteen weeks During that period they were given complementary feeds Fourteen developed gastro-intestinal symptoms though they were given suitably sized feeds They became restless, cried excessively, regurgitated and even frequently vomited food and slept for only short periods at a time The severity and duration of their symptoms varied from case to case but tended to become worse as the mother's milk yield fell It was found that these infants behaved better after vomiting the breast milk Nevertheless they did not behave as well as when they were given a complete bottle feed without a preliminary breast milk feed It was thought that the symptoms might possibly be due to the infant swallowing excessive amounts of air while sucking at an empty breast *To exclude this possibility the infant* was *given a bottle* feed of the suspected breast milk Such infants developed gastro-intestinal symptoms similar to those experienced when taking milk direct from the breast It was therefore apparent that the symptoms were not due to air swallowing or sucking at an empty breast It was concluded that infants who react to their mother's milk in this way should be artificially fed

The substance or substances in milk which may produce gastro-intestinal disturbances in the breast fed infant have been looked for during the past thirty years Some investigators noted that such milk had a relatively high chloride content (Sisson and Denis, 1921, Courtney and Brown, 1930), or a high percentage of protein (Carter and Richmond, 1898, Wardlaw and Dart, 1912), or was exceptionally rich in fat (Holt and McIntosh, 1940, Reinhold, 1948) The toxic effect of these substances was not proved More recently, however, it has been shown that toxic substances can be produced by the abnormal metabolism of fat (Agduhr, 1925 and 1927, Harris and Moore, 1929, Harris and Innes, 1931), and carbohydrate (Kermack, Lambie and Slatter, 1927, Voct-Moller, 1931, Haynes and Weiss, 1940), the former occurring in experimental animals after codliver oil and vitamin six months was ascertained and recorded in Table I It is apparent from the figures for the two groups that 59 per cent of infants in group A and 47 per cent in group B were breast fed for six months The difference between the percentages is not statistically significant Therefore it seems that the duration of breast feeding does not bear a relationship to the rate at which an infant regains his birth weight

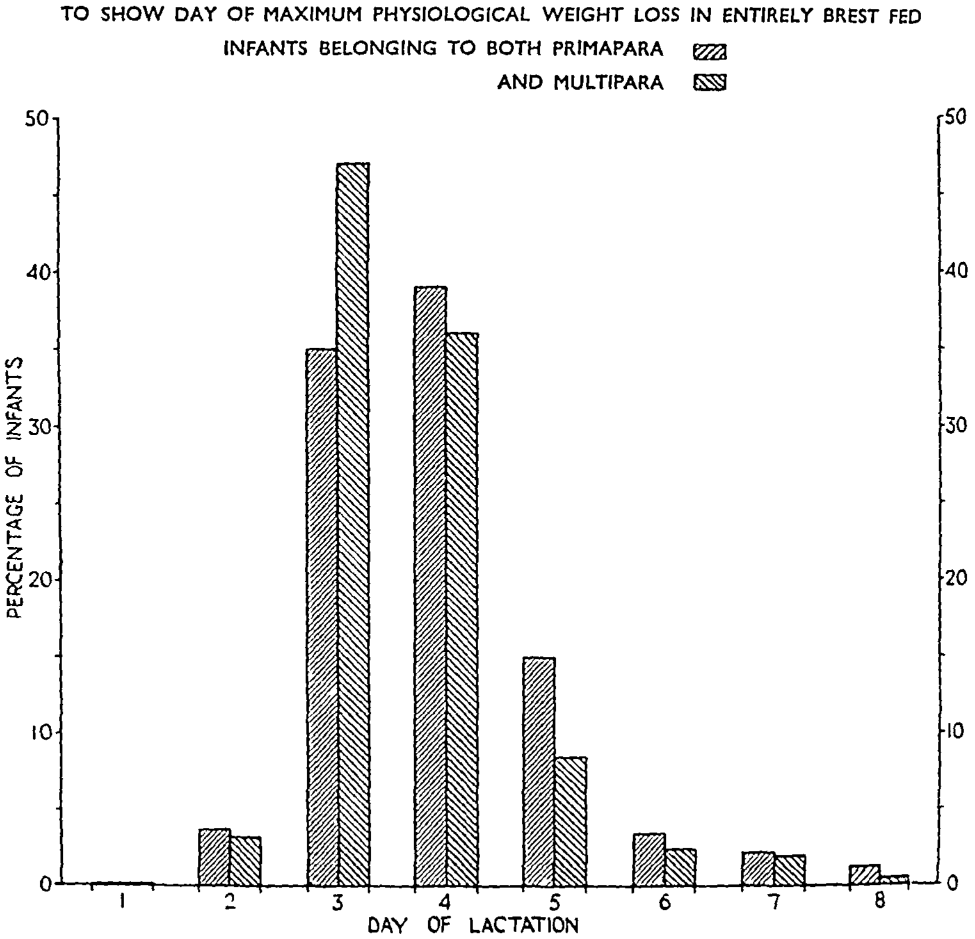

FIG 2

(b) *Routine Weighing after the Tenth Day of Life* —Many mothers like to have their infants weighed at weekly intervals during the first six months of life This procedure is encouraged at infant welfare centres because the information gained is of great value in assessing the infant's health and correct caloric requirements When utilising the results it is essential to take into consideration the various factors which affect the infant's weight progress and to know the amount an apparently healthy breast fed infant should weigh when one, two, three, four, five and six months old These weights can be readily calculated from the figures given in Table II, where the average amount of weight a mature newborn infant gains in four, eight, twelve, sixteen, twenty and twenty-six weeks has been given

In 67 per cent of cases this weight falls between two levels, namely the "confidence" limits (Table II) The values given in Table II are applicable to any mature infant because its weight progress after the second week of life is not influenced by its birth weight (Table III) The weight of both male and female infants can be taken from these figures though male infants on the average gain weight slightly faster than female infants (Boyd, 1948) An infant whose weight falls below the 67 per cent "confidence" limits must be supervised carefully and the possibility of underfeeding should be considered Moreover any infant who fails over a period of two weeks to make half the weight progress expected of him (Table III) must be suspected of being underfed

TABLE I

The Duration of Lactation in Women whose Infants (a) *Regain their Birth Weight on the Tenth Day of Life*, (b) *Fail to Regain their Birth Weight on the Tenth Day of Life*

Women with Infants	Number of Women	Percentage Breast Feeding in Months						
		½	1	2	3	4	5	6
A	116	100	94 0	75 9	70 7	67 2	62 1	59 5
B	211	100	87 2	72 0	60 2	54 5	52 6	47 4

TABLE II

The Weight Gain of 247 *Breast Fed Infants in the First Six Months of Life*

Age in Weeks	Average lb oz	S D oz	Range to Include 67 per cent of Infants	
			lb oz	lb oz
4	1 0	9	0 7	1 9
8	3 1	14	2 3	3 15
12	4 13	18	3 11	4 15
16	6 4	20	5 0	7 8
20	7 8	22	6 2	8 14
26	9 2	25	7 9	10 11

Test-weighing

Test-weighing of infants over a twenty-four hour period is indicated when they are not gaining weight satisfactorily or under feeding is suspected From the data obtained the infant's daily milk intake is calculated and compared with the theoretical amount necessary for its weight and age On the fifth day of life a mature infant requires about 1½ ozs of milk per lb body weight and an infant of this age who obtains less than 1 oz per lb body weight should be given complementary feeds Similarly, on the eighth day of life the mature infant requires about 2 ozs of milk per lb body weight and those obtaining less than 1½ ozs per lb should be given complementary feeds Infants of fourteen days old or more should have 2 to 2½ ozs of breast milk per lb body weight each day and those failing to obtain this amount usually require complementary feeds, though a few thrive on less than this theoretical amount Exceptions to this rule do occur, for very occasionally infants require more than 2½ ozs per lb body weight before it is contented

TABLE III

The Increase of Weight over Four Week Periods for Infants of Different Birth Weight

Age of Infant in weeks	Mean Weight Gain in Ounces for Infants with a Birth Weight of			All Cases (247 cases)
	lb —lb oz 6 6 15 (67 cases)	lb —lb oz 7 7 15 (112 cases)	lb —lb oz 8 8 15 (68 cases)	
1 4	16 8	16 0	14 0	15 7
5 8	33 9	32 9	31 4	32 7
9 12	29 0	27 4	27 3	27 8
13 16	22 1	22 9	23 7	22 9
17 20	20 9	19 8	20 9	20 4
21 24	16 3	18 4	19 1	18 0

Test weighing sometimes gives misleading information unless the milk remaining in the breast after the infant has fed be taken into account Some women have large amounts of residual milk because they have an abnormality of the nipple or milk sinus which prevents a free flow of milk In others the breast is not emptied because the infant does not suck properly when put to the breast To detect the existence of such difficulties both the breasts and the technique of breast feeding in all cases of suspected inadequate lactation should be carefully checked

THE CHLORIDE AND ELECTRICAL CONDUCTIVITY TESTS

The estimation of either the chloride content or electrical conductivity of breast milk in women suspected of inadequate lactation is of practical value and should be carried out on milk from both breasts when it is not possible to test-weigh the mother's infant (Miller, 1951) The results of these estimations may also indicate the probable duration of lactation (Miller and Jackson, 1951) The method of estimation of both the chloride content and the electrical conductivity and the factors which may influence the results are described by Kermack and Miller (1951*a* and *b*)

Milk chloride values which exceed 112 mg per cent in women in the second week of lactation, or 75 mg per cent in women in the third and fourth week of lactation, or 60 mg per cent in women in the second to sixth month of lactation are suggestive of inadequate lactation It is important to obtain these values for milk from both breasts before suggesting the diagnosis of inadequate lactation and it has been shown that the higher the values the greater is the chance of the diagnosis being correct In a few cases high chloride values may be obtained from one breast only These mothers should be kept under close observation and their infants weighed more frequently in order to obtain sufficient information to give a diagnosis and correct treatment It is possible, however, to detect by these tests the majority of women whose infants fail to thrive because of inadequate lactation

Measurement of the electrical conductivity of milk is as simple and informative as the estimation of the chloride content of milk Conductivity values suggestive of inadequate lactation are those exceeding 270×10^{-5} ohm^{-1} cm^{-1} for women in the second week of lactation, 225×10^{-5} ohm^{-1} cm^{-1} for women in the third and fourth week of lactation, and 210×10^{-5} ohm^{-1} cm^{-1} for women in the second to fifth month of lactation, the values being for milk at 18° The assessment of the results of the test depends, as in the chloride test, on the height of the values obtained and on whether they are obtained from both breasts, those mothers with only one abnormal breast requiring further investigation before a diagnosis is made

Routine estimation of the milk chloride or electrical conductivity of women in the second to fourth week of lactation will help the pædiatrician to predict the duration of lactation For at least 70 per cent of those women who have a milk chloride value of over 100 mg per cent or an electrical conductivity value of over 250×10^{-5} ohm^{-1} cm^{-1} at 18° stop lactating by the time their infants are two months old Women with lower electrical conductivity values lactate for a longer period

SUMMARY

Various symptoms and signs of inadequate lactation have been described and an explanation for some of them has been given Recognition of the different clinical pictures of inadequate lactation was shown to be of value in assessing the probable duration of the lactation

Routine weighing of an infant, both during and after the first ten days of life was advocated since it was possible to assess adequacy of lactation from the results Clinical investigations showed that the following findings in an infant's weight chart were highly suggestive of underfeeding loss of weight after the fifth day of life, failure to gain weight by the eighth day of life, a weight gain over a period of two weeks which was half the expected amount, and an infant with a weight below the lower " confidence limits "

Test-weighing was also found invaluable in investigating infants who were suspected of being underfed Evidence was collected which

THE VITAMIN B COMPLEX AS A SUPPLEMENT IN INFANT FEEDING

By J A CHALMERS, M D, F R C S, M R C O G
The Royal Infirmary, Worcester

In spite of Oliver Wendell Holmes' famous dictum that " a pair of substantial mammary glands have the advantage over the two hemispheres of the most learned professor's brain in the art of compounding a nutritive fluid for infants," it is suggested to-day increasingly often that both breast milk and cows' milk may be defective in various vitamins, and consequently all sorts of supplements have been recommended

Clements (1949) considers that human milk should by natural design be the ideal food for the young infant if the condition of the mother is satisfactory, and Jeans and Marriott (1947) state that the milk of a healthy woman contains sufficient amounts of all the nutritional factors necessary except iron, vitamin D and possibly thiamine With regard to vitamin B complex requirements Crosse (1949) states that little is known, and in a recent paper on infant feeding Evans (1950) makes no reference to vitamin B Sherman and Smith (1931) state that milk is relatively rich in the heat-stable factors of the vitamin B complex although Daniels and Brooks (1937) have pointed out that considerable amounts may be lost in sterilisation and even in pasteurisation On the other hand, Bicknell and Prescott (1946) state that milk is a poor source of vitamin B, and Kasdon and Cornell (1948) describe both human and cows' milk as deficient in the vitamin B complex Litchfield *et al* (1939) observe that in breast as well as in cows' milk the vitamin B complex, especially thiamine, may be in too low concentration for the optimal wellbeing of the infant, and Macy *et al* (1927) considered that pooled human breast milk from mothers receiving an average American diet was deficient in the vitamin B complex

During pregnancy, lack of vitamin B complex may lead to fœtal malformation (Mussey, 1949) and this may also give rise to anorexia, loss of weight and severe digestive disturbance in the children with lowering of resistance to infection (Kretchmer and Bayandina, 1948), and limitation of growth (Morgan and Barry, 1930) Vitamin B is necessary for carbohydrate metabolism and probably also for protein metabolism (Hess, 1917, Price, 1940) and an adequate supply of thiamine is particularly important where the diet is rich in carbohydrate and poor in fat (Crosse, 1949) In marasmic infants it increases the child's interest in its food (Price, 1940) and in premature children, at least, it helps in the retention of fluids (Litchfield *et al*, 1939)

The mammary gland derives its vitamin B from the blood, and there is consequently a wide variation in the amount supplied by milk dependent upon the mother's diet (Jeans and Marriott, 1947) This has been stressed by recent figures from Germany (Langendorfer, 1948 , Wolffram, 1948 , Dean, 1950) showing that post-war malnutrition delayed the return to birth weight of breast-fed infants The effect of maternal diet on the vitamin B intake of the infant is strikingly illustrated in a report from a Pacific island where the prohibition of an alcoholic beverage made with yeast was followed by an acute fulminating type of beri-beri with a 50 per cent mortality among breast-fed infants It was clear that the beverage had been the main supply of thiamine in the maternal diet and when it was allowed once more the infant mortality fell to 7 per cent

With regard to the requirements of the individual factors of the vitamin B complex, Gilder (1950) states that thiamine deficiency leads to anorexia and nausea, but that the effects of deprivation of riboflavin and nicotinamide are still uncertain Clements (1949) observes that significant quantities of thiamine derived from the maternal blood are found in the fœtus and that the placenta traps both thiamine and nicotinamide and secretes them to the fœtus so that its blood level may be higher than the maternal In addition there may be extensive synthesis of various factors by intestinal bacteria, a process which may be inhibited by altered bacterial flora or such factors as sulphonamide medication or anti-vitamins The administration of isolated members of the vitamin B complex may lead to signs of deficiency of others, and therefore it is better that the main B vitamins be given together (Sydenstricker, 1940) In the first two months an infant requires less thiamine from milk possibly because of its stored thiamine as well as from endogenous synthesis (Slater and Rial, 1942) While the thiamine content of breast milk is probably lower than that of cows' milk there is a greater synthesis in the gut of the breast-fed infant, and in the case of nicotinamide up to 80 per cent of the requirements may be met from this source (Ellinger and Bensch, 1945 , Holt *et al* , 1949)

A number of investigations have been undertaken, largely in the United States, to assess the requirements for infants of the various factors of the vitamin B complex Dennett (1929) found a significantly greater weight gain in infants given vitamin B complex for five months as compared with a control group, an observation which was confirmed by Bloxsom (1929) Litchfield *et al* (1939) found an earlier and greater weight gain in children given a yeast extract, and Price (1940) observed that a vitamin B adsorbate significantly increased the growth rate Kasdon and Cornell (1948), using an aqueous preparation from birth in a series of 108 infants, found no difference for three days after birth as compared with 138 controls By the seventh day, however, the test group showed a considerable improvement, the weight gain being 20-50 per cent greater By the tenth day 80 per cent of the test infants had regained or exceeded the birth weight as compared with 59 per cent of the controls, and Litchfield *et al* (1939) gave corresponding figures of 55 and 8 per cent respectively Taracena del Pinta and Garrido Lestache Cabrera (1949) found that when wheat germ containing an abundance of vitamin B complex was given to 44 infants they gained weekly an average of 84 27 per cent more weight than when the wheat germ was omitted from the diet On the other hand, Elias and Turner (1936) found that brewer's yeast failed to improve the weight gain of infants, and Clements (1949) considered that where the maternal diet was satisfactory a supplement of vitamin B complex should be unnecessary

TABLE I

Content of Various Factors of Vitamin B Complex in Infant Foods (microgrammes)

	Thiamine	Riboflavin	Nicotinamide	Authority
Human milk—100 g or 100 ml	4 8 132	16 52	260	Garrod *et al*
	9 15	28 62	66 330	Slater and Rial
	14	37	183	Macy, Williams *et al*
	15 20			Holt *et al*
	20	260		Bicknell and Prescott
	20	1600 5200		Neuweiler
Cow's milk—100 g or 100 ml	19 26	10,000 15,000		Neuweiler
	35 40	150	80 90	Slater and Rial
	35 40			Holt *et al*
	40 50	80 1000		Bicknell and Prescott
	45 75	100 300	500 1400	Garrod *et al*
	46	150	170	Macy, Williams *et al*
National dried milk (1 oz)—				
whole	85	330	200	Scientific Adviser's Division Ministry of Food
partially skimmed	100	390	280	

Table I shows the vitamin B complex content of foods commonly used in this country at present for infant feeding In each case the source of the figures has been indicated and it will be seen that there is a very wide range in the figures given by the various authorities This is probably due to regional and national variations in the diet of the milk producers concerned The figures have been converted to microgrammes and the very small inaccuracy due to the unit difference between 100 gm and 100 millilitres has been disregarded

In Table II an attempt has been made to estimate the daily intake of the vitamin B complex factors by young infants Both Ford (1949) and Clements (1949) give a figure of 2½ fluid oz (70 ml) per lb body weight as the optimal daily intake in the breast-fed infant, but in practice it has been found that the average intake has been about 15 oz (425 ml) for a child of about 7 lb On the basis of an average figure from Table I it is considered that a breast-fed infant will receive 85 mg of thiamine, 170 mg of riboflavin and 850 mg of nicotinamide (Clements (1949) gave figures of 59-112, 180-400 and 430-2152 mg respectively during the first four weeks) When these figures are compared with the theoretical daily requirements it appears that there is a considerable deficiency of all these factors in the three types of feeding considered, although Clements (1942) showed that an infant could thrive on a daily thiamine intake of 65 mg Growth was interfered with if the intake was lower than 50 mg In view of this theoretical deficiency an experiment has been undertaken in which a vitamin B complex supplement has been given to infants from birth and their progress compared with a similar number of controls whose management was in every respect the same apart from the supplement The preparation chosen was Elixir Beplex (Wyeth) which corresponded most nearly in its composition to that used by Kasdon and Cornell (1948) in their similar experiment A daily dose of 4 ml was used which supplied thiamine, 500 mg , riboflavin, 1000 mg , nicotinamide, 5000 mg This more than covered the theoretical daily requirements of these factors It was administered in one of the artificial feeds or in an ounce or so of water between feeds in breast-fed infants Very little difficulty was encountered in administration although on one or two occasions the supplement was vomited The treated group consisted of 188 infants and the control of 192

TABLE II

Estimated Daily Intake and Requirements of Vitamin B Complex Factors (microgrammes)

	Thiamine	Riboflavin	Nicotinamide
Human milk—15 fl oz (425 ml)	85	170	850
Cows' milk—15 fl oz (425 ml)	170	850	500
National dried milk (1½ oz)—			
whole	128	495	300
partially skimmed	150	585	420
Daily requirements	160 200 (Holt) 400 (Knott)	600 (USNRC)	4000 (Bicknell)
Daily experimental supplement	500	1000	5000

TABLE III

Type of Feeding

Group	Number of Infants	Number Breast Fed	Number Artificially Fed	Percentage Breast Fed	Percentage Artificially Fed
I Rosedene treated	108	84	24	80	20
II Rosedene control	105	83	22	79	21
III Raigmore treated	80	40	40	50	50
IV Raigmore control	87	55	32	63	37
V Total treated	188	124	64	66	34
VI Total control	192	138	54	72	28

infants Of these, 108 treated cases and 105 controls were derived from Rosedene Maternity Hospital and 80 treated cases with 87 controls from Raigmore Hospital, Inverness

Table III shows the type of feeding for each of the four groups and for the total test and control series In all cases considered in this paper the artificial feed used has been partially skimmed National Dried Milk It will be noted that artificial feeding has been used much more frequently at Raigmore Hospital (groups III and IV) than at Rosedene Hospital (groups I and II) The explanation is, firstly, that all tuberculous cases and a majority of unmarried girls in whom breast-feeding was avoided for medical or social reasons were treated at Raigmore Hospital Secondly at Rosedene an attempt has been made to persist with breast-feeding even if it is at first unsatisfactory, whereas at Raigmore Hospital, if adequate lactation is not established early, a readier change is made to an artificial feed This, as will be seen, gives better overall results in the first ten days of life although later it is found that the Rosedene children overtake the others

TABLE IV

Stay in Hospital and Weights of Infants (pounds)

Group	Average Stay (days)	Average Birth Weight.	Average at 3 days	Average at 7 days	Average at 9 8 days
I	9 8	7 55	7 17	7 31	7 45
II	9 5	7 9	7 5	7 7	7 9
III	10 3	7 51	7 23	7 42	7 59
IV	10	7 59	7 29	7 48	7 7
V	10	7 53	7 2	7 36	7 44
VI	9 7	7 76	7 49	7 6	7 8

The weight after 9 8 days was calculated by taking the total gain after the 7th day in each group Thence the average gain per child per day after the 7th day was calculated and the average gain in 2 8 days after the 7th This method is accurate enough when the total range of the average stay in hospital is only 0 5 days

Table IV shows the average stay in hospital and the weights of infants at birth, at three days, at seven days and at discharge in each group The average stay in hospital was 9 8 days with a range of 9 58-10 3 days All children in hospital less than seven days were excluded from consideration as were all children under 5 lb in weight, and the largest child in the series weighed 9 lb 12 oz at birth It is obvious on studying Table IV that the treated groups I, III and V, show no advantage over the controls, II, IV and VI, and in each instance there is a small difference in favour of the control groups which is not significant

Table V giving the numbers returning to or exceeding their birth weight by the seventh day also shows that there is no advantage for the treated groups This is in direct contradistinction to the findings of Kasdon and Cornell (1948) and Litchfield *et al* (1939) as there is a small advantage for the artificially-fed child in every group

Table VI shows the losses and gains in weight as a percentage of the birth weight The figure for the average loss on the third day is about half of the 7½ per cent which Langerdorfer (1948) found in his post-war series of German women suffering from malnutrition and the figures for the seventh day in this series are considerably lower than the 3 9 per cent deficit which he found on the ninth day By the date of discharge (9 8 days) in this series, groups III and IV on the average surpassed their birth weight and the deficit for all children was very small indeed and equivalent to 0 23 per cent of the total birth weight

TABLE V

Numbers Returning to or Exceeding Birth Weight at 7th Day

Group	Breast Fed	Artificially Fed	Total
I	8 (9 per cent)	5 (21 per cent)	13 (12 per cent)
II	20 (23 per cent)	8 (36 per cent)	28 (27 per cent)
III	13 (32 5 per cent)	17 (42 5 per cent)	30 (37 5 per cent)
IV	20 (36 per cent)	15 (47 per cent)	35 (40 per cent)
V	21 (17 per cent)	22 (34 per cent)	43 (23 per cent)
VI	40 (29 per cent)	23 (42 6 per cent)	63 (32 per cent)

TABLE VI

Loss or Gain in Weight (Percentage) of Birth Weight

Group	At 3 days	At 7 Days	At 9.8 Days
I	−5 03	−3 18	−1 32
II	−5 07	−2 53	−0 00
III	−3 73	−1 2	+1 65
IV	−3 95	−1 45	+1 45
V	−4 38	−2 26	−0 93
VI	−4 48	−2 06	+0 51

CONCLUSIONS

In this study of 188 infants to whom a vitamin B complex supplement was administered during the first ten days of life no advantage of weight gain was found at any stage as compared with a control series of 192 infants in whom management was identical apart from the administration of the supplement Although theoretical considerations would indicate that both human and cows' milk, as well as National Dried Milk, are unlikely to supply enough of the vitamin B complex factors for the needs of the infant, and many feeding experiments have shown greater and more rapid weight gain in new-born infants to whom supplementary vitamin B complex has been administered, the expected advantage in the treated series was not found in this study The explanation of this is probably in the adequacy of the intake of vitamin B complex in the present maternal diet in the North of Scotland Yudkin (1950) has stated that in spite of the surplus of many foodstuffs to be found in the United States, a higher proportion of people there, as compared with Britain, shows obvious nutritional deficiency, and it may well be that the improved growth rate described by Kasdon and Cornell (1948) and many other American authors is a reflection of this fact Clements (1949) has pointed out that thiamine, derived from the maternal diet, is to some extent stored by the infant towards the end of the uterine life and that consequently demands for thiamine from the mother may be lower during the first two months of life In premature infants, on the other hand, the storage of thiamine and other vitamin B complex factors has not taken place to the same extent, and the efficiency of synthesis by intestinal bacteria is probably lower so that in these there is still a need for supplementary vitamin B In the mature infant in this country unless there has been some deficiency in the maternal diet the addition of vitamin B supplements to the feeds in the first days of life appears to offer no advantage

SUMMARY

1 Theoretical considerations suggest that both breast-fed and artificially-fed infants may suffer from deficient intake of vitamin B complex

2 A supplement affording, thiamine—500 mg , riboflavin—1000 mg and nicotinamide—5000 mg , has been given to 188 infants which have been compared with a control series of 192 infants whose management in other respects has been identical

3 No advantage has been found in the treated groups at any stage during the first ten days of life and it is considered that this is due to adequate vitamin B intake by the mother during pregnancy with consequent ample storage by the fœtus in the late weeks of pregnancy It therefore appears that such a supplement is unnecessary

4 The deficient storage in premature infants suggests that in these, results should be improved by the administration of a vitamin B complex supplement

I am indebted to Miss Campbell of Rosedene Hospital and Miss Walton of Raigmore Hospital for the care with which they have carried out the additional work involved in this study , to Miss G Z Brewster of the Scientific Adviser's Department of the Ministry of Food and Miss Audrey Z Baker of Vitamins Limited for information about the factors of vitamin B complex , and to Mr G L Frewin and Mr Ross Martin for help in the interpretation of the figures obtained

BIBLIOGRAPHY

BICKNELL, F , and PRESCOTT, F (1946), *The Vitamins in Medicine*, London, Heinemann

BLOSSOM, A P (1929), *Amer Journ Dis Child*, 37, 1161

CLEMENTS, F W (1942), *Med Journ Aust*, 1, 12

CLEMENTS, F W (1949), *Infant Nutrition*, Bristol John Wright & Son

CROSSE, V M (1949), *The Premature Baby*, second edition, J & A Churchill, London

DANIELS, A L , and BROOKS, L (1927), *Proc Soc Exper Biol & Med*, 25, 161

Dean, R F A (1950), *Proc Roy Soc med*, 43, 273

Dennett, R H (1929), *Journ Amer med Assoc*, 92, 769

Elias, H L and Turner, R (1936), *Journ Pediatr*, 8, 352

Ellinger, P, and Bensch, R (1945), *Lancet*, 48, 432

Evans, P (1950), *Brit Med Journ*, 1, 1128

Ford, F J (1949), *Lancet*, 1, 987

Garrod, Batten and Thursfield (1949), *Diseases of Children*, 4th Edition, Ed Paterson, D, and Moncrieff, A, London, Arnold, 2, 194

Gilder, S S B (1950), *Brit Med Journ*, 1, 341

Hess, A F (1918), *Amer Journ Dis Child*, 13, 98

Holt, L E, Nemir, R L, Snyderman, S E, Albanese, A A, Ketron, K C, Guy, L P, and Carretero, R (1949), *Journ Nutrit*, 37, 53

Jeans, P C, and Marriott, W M (1947), *Infant Nutrition*, 4th Edition, St Louis, C V Mosby Co

Kasdon, C, and Cornell, E L (1948), *Amer Journ Obst & Gyn*, 56, 853

Knott, E M (1936), *Journ Nutr*, 12, 597

Kretchmer, B B, and Bayandina, S A (1948), *Pediatriya*, 6, 12

Langenforfer, G (1948), *Arch Gynak*, 70, 1146

Litchfield, H H, Lichterman, J, Knoll, I, and Kurland, I (1939), *Amer Journ Dis Child*, 57, 546

Macy, I G, Outhouse, J, Graham, A, and Long, M L (1927), *Journ Biol Chem*, 73, 189

Macy, I G, Williams, H H, Pratt, J P, and Hamil, B M (1945), *Amer Journ Dis Child*, 70, 135

Morgan, A F, and Barry, M M (1930), *Amer Journ Dis Child*, 39, 935

Mussey, R D (1949), *Amer Journ Obst Gyn*, 57, 1037

Neuweiler, W (1937), *Klin Wochschr*, 16, 1348

Price, M R (1940), *Brit Med Journ*, 2, 80

Report on Nutrition, (1945, U S National Research Council

Sherman, H C, and Smith, S L, *The Vitamins*, second edition, 1931, New York, Chemical Catalog Co, New York

Slater, E C, and Rial, E J (1942), *Med Journ Aust*, 1, 3

Sydenstricker, V P (1940), *Journ Amer Med Assoc*, 114, 2437

Taracena del Pinta, T, and Garrido Lestache Cabrera, J (1949), *Acta Pediatr esp*, 7, 847

Wolffram, E (1948), *Arch Gynak*, 70, 1155

Yudkin, J (1950), *Brit Med Journ*, 1, 1101

OBITUARY

GEORGE LYALL CHIENE

M B, F R C S E

Mr George Lyall Chiene died very suddenly at his home in Edinburgh on the evening of 19th November 1951, at the age of 78, though apparently in his usual state of health in the afternoon

The elder son of the late John Chiene, Professor of Surgery in Edinburgh University, he was educated at the Edinburgh Academy, from which he proceeded to Christ's College, Cambridge Returning to Edinburgh for his medical studies, he graduated M B , C M , in 1897 In the course of the following two years he was house physician to Sir Thomas Grainger Stewart, and house surgeon to Professor Annandale In the spring of 1900, during the South African War, he went out as Assistant Surgeon in the Edinburgh and East of Scotland Hospital, but in the autumn of the same year this hospital was taken over by the Military Authorities, and the staff returned home , with Mr (now Sir) David Wallace he wrote the Report of that hospital

In 1901 he became a Fellow of the Royal College of Surgeons of Edinburgh, and was appointed Assistant Surgeon to the Royal Hospital for Sick Children He was Junior Assistant for a year, and then Senior Assistant for about five years, to his father in the University Department of Surgery , thereafter for many years to held a successful class on Surgery in the Edinburgh School of Medicine He was elected Assistant Surgeon to Edinburgh Royal Infirmary in 1903, on the same day as Archibald Scot Skirving , succeeded to the charge of wards as full Surgeon in 1922 , and retired in 1937 on completion of the statutory fifteen years He had been President of the Royal Medical Society of Edinburgh, and later of the Medico-Chirurgical Society of Edinburgh

On the institution of the Territorial Force in 1908 he was appointed Captain in the 2nd Scottish General Hospital, and in the first world war he served in that hospital at Craigleith till in 1918 he was sent as Acting-Major to France In the second war he emerged from retirement to take charge of the two Royal Infirmary annexes at Corstorphine

Chiene was recognised as an excellent general surgeon In 1904 he introduced in Edinburgh the use of " stovaine " as a spinal anæsthetic, and in 1923 he published a popular *Handbook of Surgery* His special operative procedures included division of both ends of the sterno-mastoid muscle in congenital torticollis, an operation for inguinal hernia, a modification of the approach to the appendix, and an operation for large midline ventral hernia by specially designed lateral incisions for the relief of tension Chiene was an exceptionally good teacher, and, like his father, taught by word and example the duty and value of a kind and homely approach to patients, often in his case with the use of the Doric, which relieved anxiety and put them at their ease In his clinical class he introduced every term a debate on a surgical subject , and he was very popular with students because of the excellence of his teaching and his ever-ready and kindly friendship

He was a good athlete in his younger days The writer, looking back upon almost seventy years of intimate friendship, remembers playing with him at the end of the eighties in the school cricket XI, and also at centre three-quarters (there were only three in these days !) with Chiene at full back He remained a good golfer and angler One of his hobbies was water-colour painting, in which he possessed real skill, and he used his artistic gift successfully in his surgical teaching

In many ways George Chiene resembled his distinguished father, and, as he grew older, the resemblance in appearance, voice and manner became even closer, and interested and delighted those who had known the Professor Chiene was in his element at informal dinners, at which he was no mean singer, and at social functions , and he possessed the charm of a simple, genial nature He is survived by his wife and two sons, to whom we offer our sympathy , and the death of George Chiene will be a very real grief to his widely scattered students and to the diminishing circle of his contemporaries

NORMAN SCOTT CARMICHAEL

M B , Ch B Ed , F R C P Ed

Dr NORMAN CARMICHAEL, consulting physician to the Royal Edinburgh Hospital for Sick Children, died at his home in 43 Moray Place, on 16th November, at the age of 68

He was throughout his life an Edinburgh man Born in Northumberland Street, he was educated at Edinburgh Academy, studied medicine at Edinburgh University and graduated M B , Ch B , in 1905 In his professional path he followed his father in combining general practice with special study of disease in children He became a Fellow of the Royal College of Physicians of Edinburgh in 1913, when he was already an Assistant Physician at the Children's Hospital During the 1914-18 European war he went to Salonika with the Edinburgh Hospital, attaining the rank of Major, R A M C , and receiving the Serbian Order of St Sava On his return home he was appointed in 1920 Physician to the Children's Hospital, and Lecturer in Diseases of Children in the University of Edinburgh He retired from the hospital service in 1935 on completion of his term of duty On the outbreak of the second world war in 1939 he again left Edinburgh for military duty at the E M S Hospital at Turnberry, Ayrshire, where he was superintendent and consulting physician At the close of the war he returned to Edinburgh, resuming his private practice, and also acting for several years as medical superintendent of Leith Hospital He was also Surgeon-Apothecary to the King at Holyrood Palace, and for many years he was a member of the Royal Company of Archers, King's Bodyguard for Scotland

His father, Dr James Carmichael, physician to the hospital, his older brother Edward, for some years assistant surgeon, and Norman himself also physician, together made a notable family contribution to the work and teaching of the Edinburgh Children's Hospital Norman was a sound and popular teacher, and he must have formed the practice and ethical standards of many generations of medical students Among his hospital colleagues he exerted a powerful influence for good , he never stirred up strife, but when contentious subjects were under discussion, the expression of his views was frank and always courteous , and in all matters his wise, honourable and friendly character gave weight to everything he said In his last years when the shadows of ill-health and family bereavement fell upon him, he showed great courage and undiminished cheerfulness By his patients in hospital and private practice and by his medical colleagues his memory will be cherished

NOTE

Royal College of Physicians of Edinburgh

AT a Quarterly Meeting of the College held on Tuesday, 5th February 1952, the President, Dr W A Alexander, in the Chair, the following were elected Fellows of the College —Charles Mann Fleming, M A, M D GLASG , Walter Henderson, M D EDIN , Henry Edmund Seiler, M D GLASG , Ian Hunter Lockhart Gillies, M D GLASG , William Hugh Galloway, M B EDIN

The following were elected Members of the College —William Boyd, M B EDIN , Irene Parker Rowlands, M R C S, L R C P, F R F P S G , Sidney Stein, B SC CAPE TOWN, F R C S, L R C P , Robert Orton, M D LEEDS, John Norman Armour, M B N Z , Grainger Wilson Reid, M B EDIN , Vincent Daniel Bayliss, B A MADRAS, M B MADRAS, Suraj Prakash, M B PUNJAB, Harold McDonald Forde, M R C S, L R C P , Nathan Gordon, M B WITWATERSRAND, Rajeshwar Prasad, M B PATNA, Balawant Mahadeo Kher, M D BOMB , Leon Albert, M B CAPE TOWN, John Gant, B SC CAPE TOWN, M B CAPE TOWN, Mahadeo Prasad Mehrotra, M D LUCKNOW, Jean Clyne Taylor, M B ABERD , Harry Black, M B N Z, M R A C P , Andrew Cairns Douglas, M B EDIN , Patrick Cushny MacGillivray, M B EDIN , Mohomed Ahmed Botawala, M B BOMB , Suresh Dhireajlal Store, M D BOMB , Robert Stuart Malcolm Douglas Inch, M B EDIN

NEW BOOKS

Syllabus of Human Neoplasms By R M MULLIGAN, M D Pp 317, with 230 illustrations London Henry Kimpton 1951 Price 52s 6d net

At first sight it is a little difficult to see the need for this book, as the subject-matter is dealt with adequately in several of the larger works on tumours But perhaps the preface indicates its scope of usefulness, where it is stated " such a volume could be of value not only as a text for the medical student, but also as a reference for the intern, the resident, and the practising physician "

Certainly it gives much condensed information about tumours with numerous appropriate illustrations But some of the statements are not very helpful, *e g* on page 11 The term malignancy is used " when the constituent cells show lack of uniformity, relatively little resemblance to the cells from which they spring invasion and metastasis " But on page 12 it is stated " although a neoplasm may be benign by slow growth and uniform histologic characteristics, position may make it malignant, as in the case of a huge retroperitoneal lipoma by endangering vital structures "

In other places, conditions not neoplastic are described without it being clear as to their relation, if any, to neoplastic processes, *e g* under the general heading of " Neoplasms of Mesenchymal Origin ", subheading " Hæmopoietic Diseases of Uncertain Status ", there appear such things as Infectious Mononucleosis, Hodgkins' Disease, Cerebrosidosis (Gaucher's disease), and allied states Again under Thyroid page 245, there are detailed descriptions of different forms of goitre but no clear indications of their relationships, if any, with thyroid neoplasms

There are numerous references to each chapter, the great majority being to American literature only

A few minor, and obvious, misprints were noted

The book is well produced and, in spite of the criticisms above, well worth perusal

Human Blood Groups and Inheritance By S D LAWLER, M D, and L J LAWLER, B SC Pp viii+85, with 6 figures Paper covered London Heinemann 1952 Price 3s 6d

Most of us who practise medicine find it difficult enough to keep up with developments in our own field without having to note progress in other departments, especially one like the study of blood groups which advances so rapidly

This small monograph written by experts belongs to a series designed for the intelligent layman and therefore well suited to the uninitiated medical man It ranges from Empedocles (*circa* 500 B C) right up to the present, showing the development of our knowledge of the blood groups To those of us brought up on the A, B, AB, and O system and the rhesus factor it is a surprise to learn that there are now nine different systems, one of them less than a year old The book is clearly written, not too highly technical and well worth the attention of the casual medical reader

The British Journal of Tuberculosis and Diseases of the Chest Edited by P ELLMAN, F R C P Pp 80, illustrated London Bailliere, Tindall & Cox Price quarterly 8s Annual subscription 30s

With the January number of this journal this publication enters its forty-sixth year in an enlarged and extended form The editorial board has been enlarged by the inclusion of representatives of Australia, New Zealand, South Africa and Canada

This successful journal devoted primarily to tuberculosis also covers diseases of the chest and carries a series of excellent papers We congratulate our contemporary and wish it continuing success

The Quiet Art By ROBERT COOPE, M D, B SC, F R C P Pp xi+284 Edinburgh E & S Livingstone 1950 Price 12s 6d net

Dr Coope, a leading Liverpool physician, offers to the profession a remarkable collection, chiefly from the writings of medical men of all ages Some are long, many are brief—sometimes only a sentence or so They cover a wide range of topics and all aspects of medicine, reflecting the varied interests of the practitioner Many are light-hearted and amusing, others epitomise wide experience and profound advice Open the book where you will and your interest is at once aroused

The Specialities in General Practice Edited by RUSSELL L CECIL, M D Pp xxi+818, with 470 figures London W B Saunders 1951 Price 72s 6d net

Let not the above title, by virtue of its American parentage, mislead the general practitioner of this country, for, in a less vast country, his field of operation is limited in comparison with the American counterpart Cecil, himself, states in the editorial that the book's fullest use will be found where " early consultation with a specialist is not feasible " As in his *Textbook of Medicine*, the book comprises of chapters subscribed by varying American specialists, encompassing the bulk of problems occurring in general practice

With regard to clarity of text and illustrations, the chapters devoted to orthopædics and minor surgery are excellent It is unfortunate, in these chapters, and those on gynæcology and obstetrics that 60 per cent of procedures require hospitalisation, and that they are therefore outwith the scope of the British practitioner

Digests of diagnoses and treatment in ophthalmology, pediatrics and urology deserve special mention, and find no British counterpart in such compressed yet lucid form It is inevitable that some of the opinions expressed will excite opposition in this country

Although expensive, this textbook surveys such a wide and useful field, that its constant daily use will repay its outlay

NEW EDITIONS

Human Anatomy and Physiology By N D MILLARD and B G KING Third Edition Pp 590 Philadelphia and London W B Saunders Company 1951 Price 22s

Experience of previous editions has helped the authors to produce in this book an excellent survey of the main processes of the body in which simple explanations of the physiology follow after covering the relevant anatomy and histology in each section

Clarity has also been helped by numerous good diagrams, many useful tables and by omitting the tedious description of animal experiments

It can be recommended as an introduction for medical students or as a textbook for courses in subjects allied to medicine

A Textbook of Pathology By ROBERT ALLAN MOORE Second Edition Pp xiii+ 1048, with 501 illustrations London W B Saunders Company 1951 Price 63s net

This edition appears six years after the first and is characterised by much revision and expansion of the original text The new material relates among other subjects to the metabolism of enzymes, infectious conditions, diseases of the aged, bony dystrophies, effect of atomic explosion and vitamins Such primarily long chapters as those on viral, alimentary and neoplastic conditions have been subdivided, while nephritic, collagenous and demyelinating diseases are now each dealt with in individual chapters Many abnormalities such as lower nephron disease, heart failure and adrenal insufficiency, moreover, are modernised on the basis of newly acquired knowledge As before, the text is supported by numerous well reproduced illustrations and selected references to the literature and is appended by an ample index The new product as a whole thus constitutes a comprehensive, up to date and stimulating treatise in human and experimental pathology with an enhanced appeal to both student and specialist

Diathermy, Short wave Therapy, Inductotherapy, Long-wave Therapy By WILLIAM BEAUMONT, M R C S, L R C P Second Edition Pp viii+ 230, with 114 illustrations London H K Lewis 1952 Price 21s net

Does the profession get the optimum value from diathermy? The principles of diathermy and the apparatus are very clearly described in this book After a short discussion on the risks and dangers a detailed and very clear description is given of the many uses of diathermy This is a most useful book for the practitioner who wants to know the scope of diathermy and also its limitations This can also be used as a textbook for the student preparing to use diathermy in practice An extensive glossary of technical terms comprises the terminal chapter

Recent Advances in Clinical Pathology Edited by S C DYKE, D M, F R C P Second Edition Pp xii+ 575, with 37 plates and 36 figures London J & A Churchill 1951 Price 40s

As in the first edition this book is divided into four sections—bacteriology, bio chemistry, hæmatology and histology—and all the newer methods used in laboratory diagnosis are fully described and their value discussed In all the sections much is found of great interest to the clinician as well as to the clinical pathologist, as for example the chapters on the Rh factor and liver function tests The plates and figures are beautifully reproduced and clear and the indexing good This new edition should prove of great value to clinician and laboratory worker alike

Clinical Laboratory Diagnosis By SAMUEL A LEVINSON and ROBERT P MACFATE Fourth Edition Pp 1146, with 221 illustrations and 13 plates, 10 in colour London Henry Kimpton 1951 Price 84s

The fourth edition of this book continues the American tradition in works of clinical pathology This compendium provides methodological detail and interpretation covering clinical biochemistry, hæmatology, immunology, serology, bacteriology, tropical diseases, milk and water analysis, histological technique and toxicology The authors say their objective is, " To present to the student, intern practising physician and medical technology, a suitable review of clinical laboratory diagnosis " Whatever may be the situation in America it is difficult to imagine this objective being realised in this country , the needs of these groups are so varied that one volume is unlikely to serve each adequately The medical technologist will benefit most from possession of the book especially if he is working in a general laboratory Much of the material is excellent and the details of method are lucid There are, however, a few strange omissions , *e g* no mention is made of vitamin B_{12} in relation to pernicious anæmia and no method is described for the estimation of urinary 17-keto-steroids, although a reference to urinary biotin determination is given

BOOKS RECEIVED

ANSON, BARRY J , M A , PH D (MED SC), and MADDOCK, WALTER G , M S , M D , F A C S Callander's Surgical Anatomy Third Edition (*W B Saunders Company, London*)	70s
BROCK, R C , M S , F R C S , F A C S Astley Cooper (*E & S Livingstone Ltd , Edinburgh*)	20s net
CLARK, W E LE GROS, F R S The Tissues of the Body Third Edition (*The Clarendon Press, Oxford*)	30s net
CLARKE, BRICE R , M D Causes and Prevention of Tuberculosis (*E & S Livingstone Ltd , Edinburgh*)	32s 6d net
DALAND, GENEVA A , B S Edited by HAM, THOMAS HALE, M D A Colour Atlas of Morphologic Hematology (*Harvard University Press, Cambridge, Mass*)	$5 00 (32s 6d) net
ELLMANN, PHILIP, M D , F R C P Essentials in Diseases of the Chest for Students and Practitioners (*Oxford University Press, London*)	30s net
Introduction by GUTTMACHER, ALAN F , M D Hippocrates on Intercourse and Pregnancy (*Henry Schuman Inc , U S A* (*New York*))	$2 50
HILL, HARRY, F R SAN I , A M I S E , F S I A Clean Milk (*H K Lewis & Co Ltd , London*)	7s 6d net
Edited by ILLINGWORTH, C F W , C B E , M D , CH M , F R C S E , F R F P S (GLAS) Textbook of Surgical Treatment, Including Operative Surgery Fourth Edition (*E & S Livingstone Ltd , Edinburgh*)	45s net
MACKEY, HERBERT O , F R C S I , L R C P I , D P H (DUB) A Handbook of Diseases of the Skin (*C J Fallon Ltd , Dublin*)	7s 6d net
MUIR, ERNEST, C M G , C I E , M D , F R C S (EDIN) Manual of Leprosy Supplement to the First Edition (*E & S Livingstone Ltd , Edinburgh*)	2s 6d net
ROBERTS, FFRANGCON, M D The Cost of Health (*Turnstile Press, London*)	16s net
SINGER, CHARLES New Worlds and Old (*Wm Heinemann, Medical Books Ltd* , *London*)	15s net
TAIT, EDWIN FORBES, M D , PH D Textbook of Refraction (*W B Saunders Company, London*)	40s
TATLOW, W F TISSINGTON, M D , M R C P (LOND), ARDIS, J AMOR, M B , CH B , D P M (BRIST & LOND), and BICKFORD, J A R , M R C S , L R C P , D P M (BRIST) A Synopsis of Neurology (*John Wright & Sons, Ltd , Bristol*)	30s Post 11d
WALKER, G F M D , F R F P S G , D C H , M R C P The Asthmatic Child Second Edition (*John Wright & Sons, Ltd , Bristol*)	2s 6d Post 2d
By Members of the Staff of Lahey Clinic, Boston Surgical Practice of the Lahey Clinic (*W B Saunders Company, London*)	75s
WECHSLER, ISRAEL S , M D A Textbook of Clinical Neurology Seventh Edition (*W B Saunders Company, London*)	47s 6d

Edinburgh Medical Journal

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ENDOGENOUS LIPID PNEUMONIA

By H. G. MORGAN, B.Sc., M.B., Ch.B.

Lecturer in Pathology, University of St Andrews, Royal Infirmary, Dundee

THE lipids causing pulmonary disease are not so often exogenous as is commonly thought. It is now well known that among the lipids which may reach the lungs by the air passages, the inhaled or exogenous lipids, there are many, whether animal, vegetable or mineral, which lead to chronic fibrosing lesions of the lung [Graef, 1939 (pathological), Freiman *et al.*, 1940 (pathological and clinical), Sodeman and Stuart, 1946 (clinical), Schneider, 1949 (clinical), Proudfit *et al.*, 1950, and Harter, 1950 (industrial cases), Losner *et al.*, 1950 (diagnostic points), Berg and Burford, 1950 (surgical viewpoints)]. Part of the purpose of this paper is to point out that lipids associated with fibrotic pulmonary disease are in many, and probably most cases, not inhaled lipids but actually *endogenous*.

TABLE I

LIPID PNEUMONIA

Exogenous	*Endogenous*
(Oil aspiration pneumonia)	(Retention granuloma)
(1) Animal oil	(1) Bronchial narrowing
(2) Vegetable oil	(2) Bronchiolar narrowing
(3) Mineral oil	

Although it has been known for long that lipid-containing phagocytes are occasionally to be found in chronic inflammations of lung, and particularly in those associated with bronchial obstruction, it remained for the workers at the Massachusetts General Hospital (Robbins and Sniffen, 1949, Waddell, Sniffen and Sweet, 1949) to emphasise the lipid-containing nature of the widespread proliferative lesion that commonly follows obstruction of the smaller air passages. In this department pathological observations similar to those of Sniffen have been made independently on a series of pneumonectomy specimens.

This series consisted of eight pneumonectomies—five with bronchial neoplasm (one adenoma), one with late unresolved pneumonia, and

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Abstracted from a paper read at a meeting of the Tuberculosis Society of Scotland held in Dundee on 15th June 1951.

two with unresolved pneumonia and chronic abscess formation—and one necropsy specimen of carcinoma In five there was lipid pneumonia obvious to the naked eye (see Table II), and all showed the histological changes illustrated by Sniffen in 1949 These are quite distinct from the pulmonary changes seen in the generalised lipidoses (Oswald and Parkinson, 1949, Thannhauser, 1950) and the latter are not further discussed here

TABLE II

Case Reference	Anatomic Diagnosis	Other Lesions	Lipid Changes
1 101/34 (necropsy)	Squam carcinoma	No gross bronchiectasis, L L L	Obvious to naked eye
2 31414/50	Squam carcinoma	Unresolved pneumonia, fibrotic stage, L L L	Found microscopically
3 32176/50	Anaplastic carcinoma	Areas of fibrosis, R L L	Found microscopically
4 32244/50	Anaplastic adeno carcinoma	Unresolved pneumonia and early bronchiectasis of R M L	Found microscopically
5 85/51	Squam carcinoma	Bronchiectasis, R M L and R L L	Obvious to naked eye
6 1697/51	Bronchial adenoma, invasive	Areas bronchiectasis and unresolved pneumonia, L L L	Obvious to naked eye
7 485/51	Unresolved pneumonia, late fibrotic stage, L L L		Found microscopically
8 528/51	Unresolved pneumonia, fibrotic stage, R U L	Several small chronic abscess cavities	Obvious to naked eye
9 1448/51	Unresolved pneumonia, late fibrotic stage, R M L	Two fairly large chronic abscess cavities	Obvious to naked eye

To gross examination, the affected lung tissue appears grey and fibrotic, with thickening of the adjacent pleura and interlobular septa, and in each case an entire lobe or major segment is involved The endogenous lipid, when abundant, is seen as a pale yellow opaque speckling, often staphyloid, clustering especially towards the periphery of the lobe and also of each affected lobule

The main histological feature of endogenous lipid pneumonia in this series is a low grade inflammation either secondary to an obstruction of the major bronchi, often with a bronchiectatic picture, or apparently confined to the bronchioles Associated with both types is a distension of the distal alveoli by masses of lipophages, forming very obvious lagoons or backwaters In these a peculiar feature is the almost complete absence of inflammatory cells among the large lipophages (which are recognisable as foam cells in ordinary paraffin sections) Lipid material, both intra- and extra-cellular, is also present in quantity in the thickened proliferated stroma which separates these congeries of lipid-filled, but neither inflamed nor fibrosed, alveoli (the lagoons) In other parts the alveolar walls may show fibrous thickening, going on to carnification Lymphoid proliferation is also common The lipid itself occurs in two intermingled forms, as small strongly sudanophilic crimson globules and as doubly refractile crystals which are only faintly sudanophilic The histochemical reaction of Schultz (Lillie, 1948), which is given possibly by all unsaturated sterols (Yoffey and Baxter, 1949, Pearse, 1951), as well as ordinary chemical analysis of the lung tissue, show that the lipid is largely of sterol nature (cholesterol and cholesterol esters) The possibility that these sterols when present in the stroma may, like paraffin oil, be irritant and lead to fibrous proliferation has also been suggested by Sniffen

Chemical Investigation of Lungs (Table III)

The lipids present were estimated in a sample of normal unfixed lung and in two samples of abnormal lung, fixed in 10 per cent formol-saline, showing fibrosis and visible lipid formation The fixed material was thoroughly washed and dried between sheets of blotting paper All these samples, weighing from 60 to 146 g, were dried *in vacuo* at 100° C to constant weight The dry material was extracted in a Soxlet apparatus first with ether and then with alcohol A sample of the dried lipid was used for estimation of free and total cholesterol by the method of Schoenheimer and Sperry (1934)

The results show that the water content of the normal and abnormal lungs is of the same order, but that there is a marked difference in the total lipid present Cholesterol and cholesterol esters together form the main constituent of the abnormal lipid The total cholesterol also forms a much higher percentage of the lipid in abnormal than in normal lung tissue, the increase being mainly in the cholesterol ester fraction

TABLE III

Analyses of Normal and Diseased Lung Tissue

	Normal	Abnormal	
		(1) Reference 528/51	(2) Reference 85/51
Water content per cent	84 7	83 5	85 0
Total lipid as per cent wet weight	0 9	3 7	2 2
Total lipid as per cent dry weight	5 8	21 5	14 9
Total cholesterol as per cent dry weight	1 2	12 4	10 8
Free cholesterol as per cent dry weight	1 2	1 8	2 3
Ester cholesterol (by difference)	0	10 6	8 5
Total cholesterol as per cent lipid	21 3	57 7	72 3
Ester cholesterol as per cent total cholesterol	0	85 0	78 0

NOTE —Of the two abnormal lobes from which samples were taken for analysis, (1) an unresolved pneumonia, showed no obvious bronchial obstruction, while (2) was distal to a bronchial carcinoma

It is a familiar fact that low grade inflammatory processes of some standing may contain large amounts of sterol, actinomycotic lesions also frequently show the presence of lipophages The histological picture in the lungs in this series certainly indicates that the inflammatory changes are of low grade, but proof of a fungal element has not been established The irritant effect of the presence of sterols in stromal tissues is known in general pathology, and the association of the interstitial lipid with fibrotic changes in these lungs suggests that the sterols (or possibly other lipids) have been exerting some such irritant effect It is still an unexplained problem why lipophages congregate in, and come to distend, groups of alveoli in which inflammatory cells are conspicuously absent

The source of the lipids is probably the inflammatory exudate, since the lipid is seen to appear first in large phagocytic cells which surround the purulent exudate in the air passages, these cells may be numerous enough to form an obvious zone Similar lipophages are scattered singly in the alveolar exudate They may well all have taken origin from histiocytes, which Thannhauser (1947) believes are capable of forming various lipids, including cholesterol

A point of clinical importance lies in the recent advocacy of the examination of sputum, lung puncture, or biopsy material in cases of chronic localised pulmonary disease It has been suggested (Losner *et al*, 1950) that if lipid is found on such examinations then the condition is an exogenous lipid pneumonia and not a carcinoma In striking contrast to this, Reingold *et al* (1950) report that in a series of 60 cases of bronchial carcinoma, 16 showed in addition what was thought to be an inhalation oil pneumonia (exogenous lipid pneumonia) It would appear that these writers were apparently unaware of *endogenous* lipid pneumonia and its frequent occurrence as the result of a bronchial obstruction The finding of even endogenous lipid is not, however, a proof of bronchial obstruction, and I can confirm Sniffen's original observation, and the recent work of Ashe *et al* (1951), that an endogenous lipid pneumonia can occur in the absence of obstruction of major bronchi The paper by Navasquez *et al* (1951) on the endogenous form of lipid pneumonia is incomplete, since they have described the lesion merely in relation to carcinoma of bronchus and apparently have not observed the other types of endogenous lipid pneumonia, or seen the work of the American pathologists on this subject One practical implication of the recognition of endogenous lipid pneumonia is that the finding of lipid in sputum or in aspirated lung material neither excludes nor specifically indicates the presence of carcinoma

SUMMARY

Lipid pneumonia may be due to the inhalation of various exogenous lipids (chronic lipoid pneumonitis, oil aspiration pneumonia, pulmonary paraffinoma, etc) It is probably true to say, however, that the commonest form of lipid pneumonia is due to the presence of *endogenous* lipids These occur focally in lungs the seat of chronic obstructive lesions of the bronchi or of the bronchioles when the accompanying inflammation is of low grade It seems clear that these

lipids in their turn lead to fibrotic changes, and it is therefore probable that many of the cases reported in the past as due to exogenous lipids were in fact of endogenous type These findings are of importance to both clinicians and pathologists in the differential diagnosis of chronic localised pulmonary disease

I am indebted to Professor A C Lendrum for his advice in this study, to Mr Martin Fallon and Dr D G McIntosh for the pneumonectomy specimens and clinical details, and to Dr R P Cook for advice and facilities in the estimation of lipid

REFERENCES

ASHE, W M, McDONALD, J R, and CLAGETT, O T (1951), *Journ Thorac Surg*, 21, 1

BERG, R, Jun, and BURFORD, T H (1950), *Journ Thorac Surg*, 20, 418

FREIMAN, D G, ENGELBERG, H, and MERRITT, W H (1940), *Arch Intern Med*, 66, 11

GRAEF, I (1939), *Arch Path*, 28, 613

HARTER, J J (1950), *Journ Thorac Surg*, 20, 539

LILLIE, R D (1948), *Histopathologic Technique*, p 163 Philadelphia and Toronto The Blakiston Company

LOSNER, S, VOLK, B W, SLADE, W R, NATHANSON, G, and JACOBI, M (1950), *Amer Journ Clin Path*, 20, 539

DE NAVASQUEZ, S J, TROUNCE, J R, and WAYTE, A B (1951), *Lancet*, 1, 1206

OSWALD, N, and PARKINSON, T (1949), *Quart Journ Med*, 18, 1

PEARSE, A G E (1951), *Journ Clin Path*, 4, 1

PROUDFIT, J P, VAN ORDSTRAND, H S, and MILLER, C W (1950), *Arch Indust Hyg and Occup M*, 1, 105

REINGOLD, I M, OTTOMAN, R E, and KONWALER, B E (1950), *Amer Journ Clin Path*, 20, 515

ROBBINS, L L, and SNIFFEN, R C (1949), *Radiology*, 53, 187

SCHNEIDER, L (1949), *New Engl Journ Med*, 240, 284

SCHOENHEIMER, R, and SPERRY, W M (1934), *Journ Biol Chem*, 106, 745

SODEMAN, W A, and STUART, B M (1946), *Ann Intern Med*, 24, 241

THANNHAUSER, S J (1947), *New Engl Journ Med*, 237, 515 and 546

THANNHAUSER, S J (1950), *Lipidoses*, 2nd ed New York Oxford University Press

WADDELL, W R, SNIFFEN, R C, and SWEET, R H (1949), *Journ Thorac Surg*, 18, 707

YOFFEY, J M, and BAXTER, J S (1949), *Journ Anat*, 83, 89

A STUDENT'S NOTEBOOK OF JAMES SYME'S CLASS OF CLINICAL SURGERY IN 1861-62

Kept by WILLIAM McNEIL, M D Ed 1864 with extracts and comments
by CHARLES McNEIL, M D Ed, F R C P Ed & Lond

IN 1861 James Syme, Professor of Clinical Surgery in the University of Edinburgh, was at the height of his power, reputation and influence His clinical lectures began on 1st May 1861 and continued twice weekly until 3rd February 1862, interrupted by summer vacation from 26th July till 6th November 1861, in this course, 163 patients, young and old, were examined, diagnosed and treated and demonstrated by Syme to his class of students, then in their second year, and studying anatomy and dissection at the same time one of these students was William McNeil of Stranraer, and his notebook with the title " Cases of Clinical Surgery by Professor Syme 1861—" is the subject of this communication

The notes are fuller than those usually made by students They go beyond the details of the diagnosis and treatment of cases They are a lively narrative of the whole scene, giving touches of personal description of the patients, and their demeanour under stress and pain, dialogues between surgeon and patient, many anecdotes and stories told by Syme and drawn largely from his own vast experience, and the essence of the subject—the demonstration of patients by a great surgeon to his students and the exposition of his principles and practice

Some extracts from this notebook are presented by the writer of this communcation, who is the son of the Edinburgh medical student of 1861 They show something of what went on in a surgical hospital ninety years ago they bring back to life the acts and words of an outstanding surgeon of his generation, also the words and reactions of his patients and the admiring audience of his students They may thus serve to justify and preserve the reputation of Syme as a great teacher

THE PATIENTS PERSONAL TOUCHES

A few extracts show one feature of the notebook, its touches of personal description of the patients, they are little trivial facts and yet they complete and humanise the surgical record and bring the scene to life

" 1st May 1861 Case 6th A little girl from Wales, aged 8, was brought in by Dr Annandale to-day She seemed in the very highest spirits, was carrying a large doll very gaily dressed, and laughed immoderately at the round of applause with which the students greeted her appearance For more than a year she had been in failing health in consequence of a large tumour which had grown to the lower jaw under her right ear "

" 21st November 1861 Case 18th A young man from Fife was first brought in to-day He had crossed the Firth this morning to obtain relief from Pr Syme , having swallowed a copper coin yesterday It seems he is the son of a wealthy German banker in Gottenburg who had sent him to Fife to learn farming A very intelligent young man "

" 27th May 1861 Case 28th A man, aet 40, came in next, and on entering very gracefully saluted the Pr From his style of salutation I should think he is a soldier His arm was bandaged " After describing the condition with Syme's remarks, the note concludes " the man on leaving, again, most politely bowed to the Professor "

" 3rd June 1861 Case 39th A child 4 years of age was next carried into the room by his Father, a small farmer in Berwickshire who had come that morning into Edinburgh a distance of 50 miles to see Professor Syme " Examination showed the case to be Hydrocele of the cord and operation was at once carried out, and the note ends " the little fellow—very beautiful, like all previous children receiving chloroform, was quite frieghtened and cried out piteously for his mamma, till the chloroform established its sway "

" 19th July 1861 Case 73rd A poor little rascal was next introduced with his arm in a sling Very wistfully he looked at Pr Syme as he was lifted by Dr Annandale and placed on the chair beside him On Pr Syme asking him how his arm had been hurt, he said, ' I fell, Sir, aff anither boy's back ' "

SYME'S STORIES

Syme in his teaching made great use of stories " to point a moral and adorn a tale "—stories drawn from his own and others' experience In the 1861-62 notebook of his clinical lectures it is fortunate that these stories are carefully and fully recorded , in themselves they are often dramatic, sometimes melodramatic, but closely relevant to and a powerful enforcement of points and principles in the case or subject under discussion Two examples are given

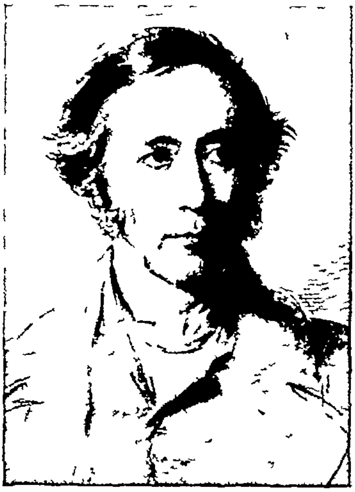
Gluteal Aneurism and Ligature of the Internal Iliac Artery — 1861 was a notable year for Syme in that two cases of gluteal aneurism presented themselves at the Infirmary within a few days of one another, and both were successfully treated by ligature of the internal iliac artery (Joseph Lister coming from Glasgow to assist at the second operation) Syme published his account of the cases in 1862 in his usual short, concise and condensed narrative , but to his students in his clinical lectures he expanded himself widely over the whole subject of aneurism, its methods of treatment, with particular application to the two present cases of gluteal aneurism , and the notebook contains a full account of the proceedings in the surgical amphitheatre, the appearance of the two cases, and their operations amid great professional interest, their progress and final cure

"16th May 1861 Case 19th A man about 25 years of age was next introduced, a strong athletic fine-looking fellow Since the beginning of January he had felt a swelling over the gluteal region. On his stripping, this looked as large as a duck's egg When Pr. Syme put his finger on the tip of the rounded swelling, the pulsation was quite perceptible *not only on the tip, but also equally over all* the swollen part This at once rendered the nature of the swelling apparent, viz an aneurism of the gluteal artery" Syme then entered on a long exposition of aneurisms in general, citing authorities and his own views and experience as to their treatment, and the lecture ended thus in the words of the notebook —"Pr Syme told another story of a farmer in Ayrshire, who having aneurism of the gluteal artery, and being very much distressed with pain sent for two qualified practitioners in his neighbourhood, who pronounced it to be an abscess and would at once proceeded to open into the supposed abscess, had not they imagined that it was not quite fit for such an operation They left, promising to be back next day and open into it That night a person, who went about the country and acted as Doctor Bone-Setter, happened to arrive at the Farmer's house and was allowed to stay all night At the usual time of retiring to rest, he was shown to bed and slept soundly till awakened early next morning before daylight, to come and let out the farmer's abscess which had become very painful In the grey light of that dark winter morning, he made the desired incision, but was surprised to find that, instead of a yellowish stream of matter as he expected, a dark purple stream was flowing rapidly from the wound Alarmed at the appearance, they sent for the two medical gentlemen already alluded to, who saw at once what had happened In vain they attempted to stop the flow of blood, which continued for two days till the Farmer died These Doctors then lodged a criminal information against the Quack who was apprehended and lodged in prison on a charge of culpable homicide The Lord Advocate referred the case to Pr Syme, who hearing all the facts thought that no criminal charge could be substantiated against the Bone-Setter, as he had acted at the wish of the Farmer, and in the same way as the two qualified practitioners themselves intended to act next day The Quack was thus saved"

In the case before us, Pr Syme intended to tie the internal iliac artery

"May 29th The operation above referred to was performed to-day The theatre crowded to the roof A great many of the Edinburgh Surgeons and Physicians present Pr Syme cool and decided as usual The Superficial (External) Iliac artery was cut in making the incision and tied, incision made very free—as soon as the operation which took about 20 minutes was over it was found that the aneurism was reduced to a third of the former size"

After further notes on the progress of the case the final report is —"19th July Case 19 was brought in to-day that we might see him before going home (John Smith, Shoemaker, Carluke) He is stiff a



James Syme

William McNeil

little still, but improving fast I saw him on the North Bridge at 3 o'clock "

Internal Hæmorrhoids—Another telling story is given when Syme was explaining and carrying out the surgical treatment of hæmorrhoids external and internal " The best remedy for such a state of matters was to remove the internal hæmorrhoids by ligature while the external, if any, should be removed by the knife " This he did in this case (71) In tying the ligatures he said " You must tie the legatures *as tightly as possible*, if you do not, your patient will suffer intolerable agony " He told us a story of a Dr N— of Inverness, who some 29 years ago had come to him in Edinburgh, seeking relief from pain endured from Internal Hæmorrhoids He was a strong powerful man, and willingly submitted to the operation of having them tied At that time it was customary to tie them so tightly as just to strangulate them Well, he had not been long operated on, when the pain became intolerable Pr Syme was sent for, and when he came found Dr N— shouting out in the wildest manner Indeed so fearful were his cries that he alarmed the whole people in the neighbourhood of the street in which he sojourned during his stay Well, to relieve him, he (Pr S) administered an opiate, and in course of time he came round, and went back to a large and extensive practice which he conducted with much ability After a time his old complaint returned, but so dreadful had been his sufferings on the former occasion that it was only when he could no longer sit with comfort that he was forced to come back to Edinburgh for relief And when he did come, the strong vigorous manly fellow was reduced to a shadow Between the period which had elapsed from his first to his second coming to Edinburgh, Professor Syme had discovered that the tighter these hæmorrhoids were ligatured the less pain was suffered, in fact he had found out the proper method of treating such growths Dr N— got the benefit of this improved method of treatment On the second occasion he suffered comparatively little, and returned to Inverness greatly improved in health, and continued up till his death to practice without a return of the complaint "

REACTIONS TO PAIN DURING SURGICAL OPERATIONS

In 1861 chloroform was being used more and more often in minor and in nearly all major operations But in quite a large number of the smaller operations, no anæsthetic was used and patients had to endure severe pain, and surgeon and students were witnesses of their sufferings The bearing and behaviour of patients, and the reactions of the non-patients under these conditions, are often mentioned in the notes Three examples are given

(1) " 21st May 1861 Case 25th A man about 60 was brought in to-day suffering from hydrocele The looks of the old fellow as he undressed were quite amusing When Pr Syme approached him with the trocar, the looks of dismay with which the patient regarded it were

irresistible Pr Syme did not give him many seconds to think he at once introduced the instrument through which a copious stream of water flowed When the fluid was drawn off Pr Syme with a syringe injected a quantity of Iodine into the bag to produce irritation The moment the Iodine was introduced, the old fellow shouted at the top of his voice and danced about as if mad Pr Syme said it was not pain that caused him to cry out , Iodine never produced pain , it was just the peculiarity of the patient, and *surprise* "

(2) " 15th July 1861 Case 69 A young man, aet 23, was next brought in, his leg (right) bent at knee and just able to touch the ground with the tip of his toes On examining the leg, Pr Syme found that the disease was confined to the Tarsus, and for 3 years the tarsus had continued thick and unyielding, but there was no tendency to suppurate Pr Syme said we would all recollect the treatment for cases of swelling that felt hard on examination and had no tendency to suppurate—the Actual Cautery He then turned to the young man and said ' I must make an opening into this Can you stand the operation without taking chloroform ? ' The young man then asked the Pr if it would be very painful The Pr said ' Oh, not very ' ' Very well,' said the young man, ' I will try it ' , little thinking of the very painful nature of the ordeal he was about to undergo The Dressers gathered round him, and the Pr told him not to look McLean brought in the red-hot iron, which was immediately applied As soon as the poor fellow felt the hot iron, he cried out ' Oh ! I wish I had taken chloroform ' He struggled in vain The Dressers held on remorselessly, and Pr S applied the hot iron until the smoke ascended to the roof of the house When it was over, Pr S asked him ' how he liked it ' ' Ah ! Sir, it was very sair ' ' Not very,' said the Pr ' Deed, it was, Sir,' said the victim as he hobbled away Pr S remarked that it was pardonable to understate to a Patient the nature of the pain that might require to be inflicted at any time in an operation "

(3) " 21st Nov 1861 Case 12 was that of an old surly-looking fellow, who was brought in, suffering from a very rare disease north of the Tweed, viz Chimney Sweeper's Cancer on Scrotum When asked by Pr Syme if he had ever been South the Tweed, he said in a very surly tone, ' Aye, I hae been in Perth ' ' Had he ever swept chimneys ? ' ' Na ! ' When asked if he would take chloroform or not, he made no reply Pr Syme with a pair of scissors at once cut out the cancer which was situated on the most dependent part of the scrotum The shouts of the old fellow were terrific Pr Syme, after he had completed the tying of the vessel cut, questioned him concerning the period of its growth, and got for a reply ' Hoo the devil can I answer ony questions just noo ? ' This created a very hearty laugh among the students, which did not improve the temper of the patient He left the theatre uttering imprecations on Pr Syme and all concerned "

These extracts and other like incidents in the notes suggests a charge of callousness in surgeon and students Without discussion of this, two quotations from " Rab & his Friends " are apposite " In them " (medical students), " pity as an *emotion* ending in itself or at best in ears and long-breath, lessens—while pity, as a *motive*, is quickened and gains power and purpose " The second quotation is after the operation on Ailie by Syme —" The surgeon dressed her, and spoke to her in his own short kind way, *pitying her through his eyes* "

" A Good Surgeon " Qualifications Medical Ethics Some General Rules

" Winter Session 1861-62 Nov 7th 1861 Professor Syme commenced his introductory address by referring to the importance of students attending to dissection , as without it, no man could hope to become a good surgeon It was only by dissecting that one could obtain a knowledge of the different organs, vascular and otherwise, of their positions and relations to each other, and it was mainly by means of it that he acquired the use of his hands in such manipulation If you cannot get human bodies to dissect, then by all means dissect the bodies of the lower animals, dogs, cats, rabbits etc He said it was quite a mistake to imagine that in order to become a good surgeon, men must be more than usually dexterous in the use of their hands No doubt manual dexterity was of some importance Yet he did not for a moment hesitate to say that more mechanical skill was necessary in the making of a chair than in almost any surgical operation "

" Another subject he especially urged upon students was the importance of adopting sound principles In order to become good practitioners we must adopt sound principles of theory and practice How many men went out into the world without any principles at all hence their want of success Let us adopt sound principles and our practice would become correspondingly sound "

Later, on 13th Jan 1862, he referred again to anatomy and emphasised its importance with another of his exciting stories " ' In order to be good surgeons you must be good anatomists ' Here the Pr told a good story of a surgeon who had been in practice for some time and yet never studied anatomy or had ever dissected a body, being called on to perform an operation for the relief of strangulated hernia The operation, which lasted nearly a day, had to be performed in a house, through the windows of which a crowd of children were staring and screaming (I failed to hear whether he had been able to give his patient the relief required without killing him) The ordeal which he had undergone, however, sent him to Edinburgh to learn anatomy This case, Pr Syme said, should make us all study anatomy diligently so as to give us confidence and ease of mind in our operations "

The next note raises delicate points of medical ethics and behaviour " He then told us of another case in which a medical man brought from a Provincial town a patient labouring under what he believed to be Hernia The other medical men in the same town also believed that it was a hernia, whilst a Quack in the same town said it was a Hydrocele Pr Syme on examining the man said that it was a Hydrocele, and on puncturing the Scrotum with a trocar showed the truth of his opinion The medical man begged Pr S to say it was a hernia as the credit of the profession was at stake, the Quack being likely to rise in the estimation of the community Pr S could not say what he believed to be untrue, but to the great joy of this medical man, the withdrawal of the water from the scrotum removed the support from the bowel above, which accordingly came down, saving the medical men's credit but proving fatal to the poor patient "

Some General Rules—In a case of severe disease of the foot in a girl, aet 14 years, Syme advised amputation of the foot "The girl as soon as she heard this, cried out—'I'll no let you take it aff,' and made for the door, which the Pr did not attempt to contradict and reason her out of simply remarking after she and her mother went out—'Gentlemen, you will find it very useful in practice never to appear to go against the mind of your patient' "

In another case "he cautioned the class to avoid the pernicious habit of operating on all and every occasion He said we ought never to operate unless we felt sure that benefit was likely to result from it "

In a case of psoas abscess he pointed out the dangers of opening this, and continued, "Now Gentlemen it is the duty of the Professional man to prolong life by all possible means, and if abstaining from doing anything comes within the category of 'possible means,' then *do nothing* What I would recommend in this case is just to *do nothing* "

JAMES SYME, JOSEPH LISTER, THOMAS ANNANDALE

A last extract shows three successive Professors of Clinical Surgery at Edinburgh operating together on the second case of gluteal aneurism "Friday, 14th June 1861 Pr Syme assisted by Pr Lister of Glasgow and Dr Annandale performed the operation today On making incision in the aneurismal sac, the Blood spouted out to a great height one jet lighted on the face of the student who administered the chloroform Pr Syme immediately introduced his finger into the opening but did not succeed in finding the artery He then enlarged the opening so as to admit his hand, but so firmly had the clotted blood of the old sac grown over it that he could not reach the artery so as to exercise the necessary pressure on it He then opened freely into the sac and at once got the vessel under command Dr A was particularly active Loss of blood was great Pr Syme thinks all will go well 'Amen!' "

The student's prayer was answered, and the patient "a man, aet 44, from the neighbourhood of Carlisle" made a good recovery

The extracts given above show something of the character and quality of this student notebook The book itself, with its 115 closely written pages in a free legible hand, is much more than an account of surgical principles and methods many of which are now obsolete—a dissected specimen dry and dead of out-of-date surgery Its pages provide in dramatic form the whole human setting of a great surgeon at work They give a day to day description of James Syme at the summit of his achievement and influence The reader can see the working of the surgeon's mind in examination, and of his hands and the instruments of his hands in operation , and hears his words, few, clear, and incisive as his knife Beside him are his assistants—the house surgeon and dressers around, on the crowded benches, his students attentive and admiring , over the head of the surgeon bending to his work the invisible but felt aura of his experience and reputation And in the centre are the patients, not mere cases tagged with their age and sex and disease but living creatures The girl, aet 8 with a large tumour on the right jaw is introduced as " a little girl from Wales, in the very highest spirits, and carrying a large doll very gaily dressed " while case 44, a woman aet 35, with a boil on the thigh, under chloroform " began to sing a hymn in praise of her Maker, which seemed to tickle the fellows very much "

Here in this notebook is life in a surgical theatre in Edinburgh in 1861 on the stage the surgeon, the assistants and the patients , in the amphitheatre the audience of students, their eyes and ears directed to the stage In this surgical drama Syme dominates both stage and audience, and conducts the play This student's notebook in its dramatic form is a valuable contemporary document of a bygone age in surgery and it draws from life a convincing portrait of James Syme as a great surgeon and a great teacher

MEGALOBLASTIC ANÆMIA OF PREGNANCY AND THE PUERPERIUM

By JAMES R CLARK, M B, Ch B, M R C P Ed
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WALTER CHANNING [1] of Boston, Massachusetts was the first to recognise the disease now generally called megaloblastic anæmia of pregnancy and the puerperium In a paper published in 1842 he distinguished it from anæmia due to loss of blood and noted its severe and often fatal character Sir William Osler [2] in 1919 in his "Observations on the Severe Anæmias of Pregnancy and the Post-Partum State" drew attention to the fact that the disease differed from Addisonian pernicious anæmia in that when recovery took place it was permanent, although recurrence in a subsequent pregnancy was possible The first description of the bone marrow in the disease was given in 1936 by Heilbrun [3] who found it closely resembled that seen in untreated Addisonian pernicious anæmia Meanwhile it was being realised that the blood picture did not always correspond exactly to that seen in Addisonian anæmia Of Stevenson's [4] 30 cases published in 1938, 12 had a colour index of unity or below unity Moreover, Stevenson found achlorhydria in only 3 cases out of 19 examined None of this series of cases had a bone marrow examination carried out, however Davidson, Davis and Innes [5] in 1942 emphasised the ways in which the disease could differ from Addisonian pernicious anæmia, and observed that it might respond poorly or not at all to treatment with refined liver extract Fullerton [6] in 1943 found a similar refractoriness to treatment with refined liver Callender [7] in 1944 reviewed the condition very fully, showed that the mean corpuscular volume might be within normal limits, and stressed the importance of marrow examination which might be the only means of establishing the diagnosis

The Hæmatological Department of the Royal Infirmary of Edinburgh under the charge of Professor Davidson has treated since 1939, 43 cases of megaloblastic anæmia of pregnancy or the puerperium Sixteen of these cases were published in 1942 [5] and 3 more in 1948 [8] Reference will now be made to 18 cases seen during the past seven and a half years (January 1944-June 1951) and the main clinical and hæmatological features of the disease will be described

INCIDENCE

Fifteen of the 18 cases were referred from the Simpson Memorial Maternity Pavilion These were distributed over the seven and a half years as shown in Table I

A Honeyman Gillespie Lecture delivered on 22nd November 1951

The second column of figures represents the total yearly admissions to the Simpson Since only hospital admissions are considered, no conclusions can be reached regarding the general incidence of the disease, but the figures will at least serve to show that it is not frequently encountered Nevertheless the 16 cases published by Davidson, Davis and Innes [5] in 1942 were seen in two years during which period there were approximately 8000 confinements in the maternity hospitals concerned

TABLE I

The Yearly Admissions to the Simpson Memorial Maternity Pavilion and the Number of Cases of Megaloblastic Anæmia Diagnosed there during the Same Period

Year	Number of Cases of Megaloblastic Anæmia	Total Admissions to S M M P
1944	3	3875
1945	2	3873
1946	2	4519
1947	0	4255
1948	1	4321
1949	2	4357
1950	2	4371
1951 To 30th June	3	2184

As to the experience of others, Evans [9] in 1929 found no case in 4000 pregnancies Boycott [10] in 1936 found no case among 222 pregnant women, and in 1937 Reid and Mackintosh [11] found none in 1108 pregnancies Thompson and Ungley [12] this year (1951) reviewed 45 cases which had been seen during the past seventeen years No data about incidence are, however, available

With regard to the relative frequency of the disease as compared with Addisonian pernicious anæmia, the commonest form of megaloblastic anæmia in this country, during the seven and a half years under review, 322 cases of the latter disease were seen at the Blood Clinic and associated wards, approximately 18 cases for every case of megaloblastic anæma of pregnancy

CLINICAL FEATURES

Age—The age varied between 21 years and 41 years, the mean age being 33 years These figures contrast, as is the rule [4, 12], with those seen in Addisonian pernicious anæmia which has its greatest incidence between the ages of 40 and 70 [17]

Previous Pregnancies—Five of the women were primigravidæ, while 12 had borne two or more children, the condition, as usual, being more commonly seen in those who have had previous pregnancies [4, 7, 12]

Diarrhœa of prolonged duration was found in 2 cases (Nos 16, 17), no specific organism being isolated in the stool of either

Œdema of varying degree is of quite common occurrence [4, 7] In 4 cases œdema was marked but 3 of these suffered from pre-eclamptic toxæmia

A Sore Tongue was complained of in 7 cases, of these, 5 were abnormal on inspection, showing either acute glossitis or atrophy of the papillæ In addition the tongue was atrophic in 6 other cases, without being sore Thus the tongue was sore and/or atrophic in 13 cases out of 18

Koilonychia was seen in no case

Enlargment of Spleen—Only 1 patient (No 13) had a palpably enlarged spleen

Enlargement of Liver was seen in 2 cases (Nos 5 and 16)

Nervous System—Examination of the nervous system revealed no abnormality except in 1 case (No 10) who exhibited a mild hemiparesis which had followed diphtheria at the age of 6 The rarity of sub-acute combined degeneration in megaloblastic anæmia of pregnancy [12] as compared to its not unusual occurrence in Addisonian pernicious anæmia, has long been recognised

Serum Bilirubin or icteric index examinations were carried out in only 3 patients, the highest figure for the latter being 11 units Some of the patients showed an apparent degree of icterus similar to that often seen in pernicious anæmia In general such an appearance is more common in the latter disease [7]

A Test Meal was carried out in all but 2 of the cases Free hydrochloric acid was found in 10 cases and a histamine-fast achlorhydria in 6 This is one of the most significant ways in which the disease differs from Addisonian pernicious anæmia where achylia is always found [13] The 6 cases with achlorhydria had atrophic tongues Of the 10 cases with free acid, only 3 had atrophic tongues

Diet During Pregnancy—A full analysis of the diet was requested from the Dietetic Department in 2 cases only (Nos 14, 15) In both the diet was found to be inadequate For example in Case 15 "the total number of calories was inadequate, the protein below the recommended allowance, calcium below normal and vitamin A only half the recommended amount Thiamine was quite inadequate and the B complex low" In addition an inadequate diet was taken by 5 patients on account of continued vomiting In another case the diet was judged to be grossly lacking in calories, first-class protein and vitamins Two patients ate little food on account of poor appetite and nausea No fault was found with the diet in 4 cases and no information is available in 3 Thus the diet during pregnancy was unsatisfactory in at least 8 cases Although this state of affairs is common [12] its ætiological significance is not established This matter will be referred to again

HÆMATOLOGICAL FINDINGS

The state of the blood in each case at the time of diagnosis is shown in Table IV

TABLE IV

Main Hæmatological Findings

Case	Hb %	Hb gm%	R B C (mil /cmm)	C I	W B C cmm	P C V %	M C V cμ	M C H C %
1	70	10 36	3 08	1 14	8,200			
2	28	4 14	1 18	1 19		13 5	114 4	30 6
3	40	5 92	1 97	1 02	8,600	17 5	88 8	33 2
4	42	6 21	2 91	0 72	5,800	19	65 3	32 6
5	38	5 62	1 45	1 30				
6	52	7 69	2 76	0 94	8,200	29	105 1	26 5
7	60	8 88	2 33	1 29	7,200	24	103 0	37 0
8	48	7 10	1 76	1 36	8,800	21	119 2	33 8
9	30	4 44	1 65	0 90	10 200	17	103 0	26 1
10	50	7 40	2 94	0 84	4,000	22	74 8	33 6
11	44	6 51	2 03	1 08	8,200	18	88 6	36 1
12	52	7 69	2 19	1 19	6,000			
13	21	3 10	1 18	0 87	6,000	10	84 7	31 0
14	35	5 18	2 13	0 82	5,600	16 5	77 4	31 4
15	50	7 40	2 78	0 91		22	79 1	33 6
16	37	5 47	1 95	0 94	4,400	13	66 6	42 0
17	58	8 58	3 50	0 82	6,200	21	60 0	40 8
18	34	5 03	2 05	0 83	5,000	16 1	78 5	31 2

P C V = packed cell volume
M C V = mean corpuscular volume
M C H C = mean corpuscular hæmoglobin concentration

It will be noted that in 2 cases (Nos 16 and 17) the M C H C was apparently higher than the theoretical maximum

Hæmoglobin —The lowest Hb was 21 per cent (3 1 gm per cent) and the highest 70 per cent (10 36 gm per cent) The mean was 44 per cent (6 5 gm per cent) (In every case standardisation was the same, 100 per cent = 14 8 gm per cent)

Red Cell Count —The lowest initial figure seen was 1 18 mil /c mm and the highest 3 5 mil /c mm In 6 cases the red count was over 2½ mil /c mm The mean figure was 2 21 mil /c mm

Colour Index —This ranged between 0 72 and 1 36 with a mean of unity (1 008) The normal range may be regarded as 0 85-1 15 [14] On this basis 5 cases had a colour index above normal, 8 had a colour index within the normal range and 5 were below it

Mean Corpuscular Volume —This was estimated in 15 cases The results varied between 119 2 cμ and 60 0 cμ with a mean of 87 2 cμ The normal range may be taken as 78-94 cμ [15] so that on this basis 5 gave figures above normal, 5 below normal and 5 within the normal range Judging from the stained film alone macrocytosis was present in 6 cases The colour index was raised in 5 of these cases and the mean corpuscular volume in 4 but no mean corpuscular volume reading was available in the other two The M C V was raised in only one case in which macrocytosis was not suggested by either the film or the colour index

By all methods employed, therefore, macrocytosis was detected in only 7 cases out of the 18

The absence of macrocytosis in a significant proportion of cases has been generally recognised,[4, 5, 7, 12] and has an obvious bearing on the problem of diagnosis

Hypochromia—The colour index is of limited value in megaloblastic anæmia of pregnancy in determining incomplete saturation of the erythrocytes with hæmoglobin A better method is to calculate the mean corpuscular hæmoglobin concentration The normal range for this is 32-38 per cent [15, 16] Six cases gave figures below this range but only 2 were below 30 per cent A degree of iron deficiency is frequently found in the untreated case [12] while in untreated Addisonian pernicious anæmia this is rare Detection of iron deficiency by examination of the stained film may present considerable difficulty Evidence of iron deficiency appeared to be seen in 6 cases, but could be correlated with the M C H C in only 3 of these Nevertheless in some cases with a dimorphic peripheral blood picture, inspection of the stained film may be of more value in diagnosis than estimation of the M C H C or colour index (Fig 1)

FIG 1—Peripheral blood—dimorphic anæmia from a case of megaloblastic anæmia of pregnancy

FIG 2—Bone marrow—showing early megaloblasts and one late megaloblast (Case 14 before treatment)

FIG 3—Bone marrow—showing an intermediate megaloblast (Case 13 after refined liver therapy and before treatment with folic acid)

FIG 4—Bone marrow—showing change to the hyperplastic normoblastic state (Case 13 following folic acid therapy)

FIG 5—Bone marrow—showing late normoblasts following folic acid therapy (Case 14) × 950

White Blood Count—A wide range of normality is recognised, 4000-11,000 [17] W B C counts before treatment are available in 15 cases, and in no case did the figures fall beyond these limits The low white counts frequently seen in pernicious anæmia were not found

No platelet counts were carried out in any of the cases None of this series showed purpura or other hæmorrhagic features

Examination of the Stained Blood Film—This procedure often failed to suggest the true nature of the anæmia As already stated, macrocytosis was well marked in only 6 cases Nevertheless the detection of an occasional macrocyte in other cases with a normal M C V was the clue to further investigation Inspection of the film was also of value in those cases with a dimorphic anæmia as already stated

Immature white cells and nucleated red cells were occasionally seen in the present series Case 8 showed a few metamyelocytes and

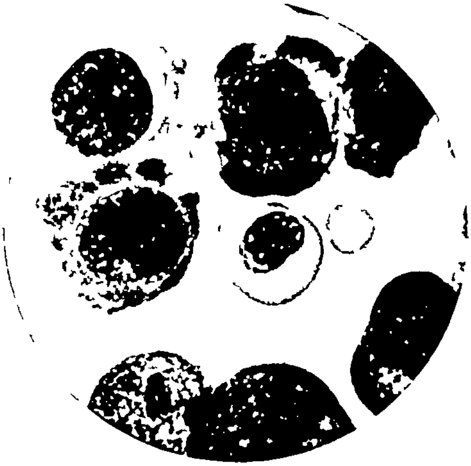

FIG 2

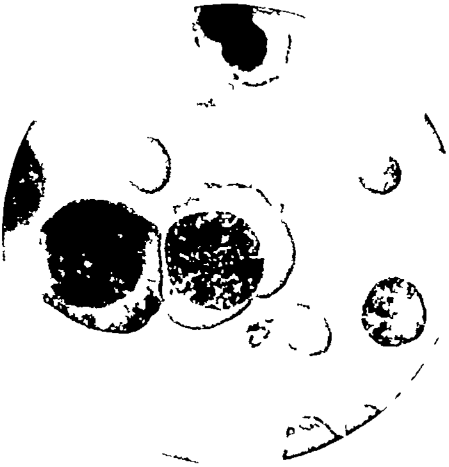

FIG 3

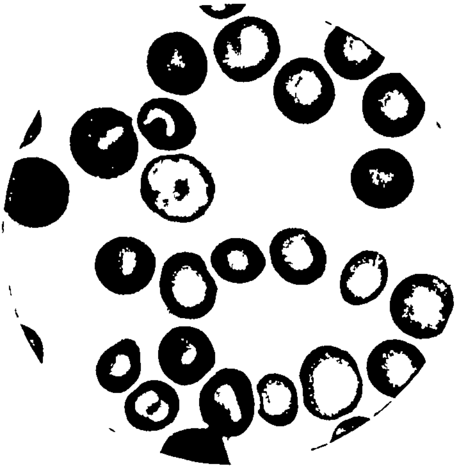

FIG 1

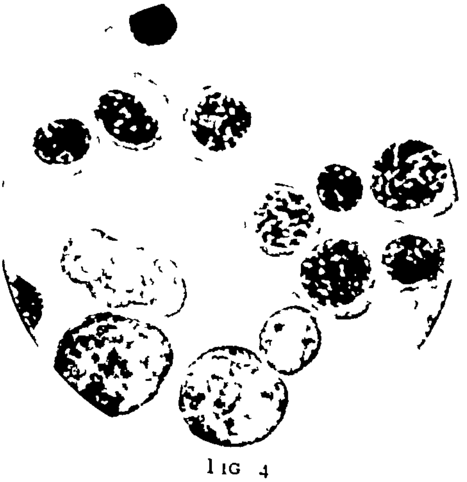

FIG 4

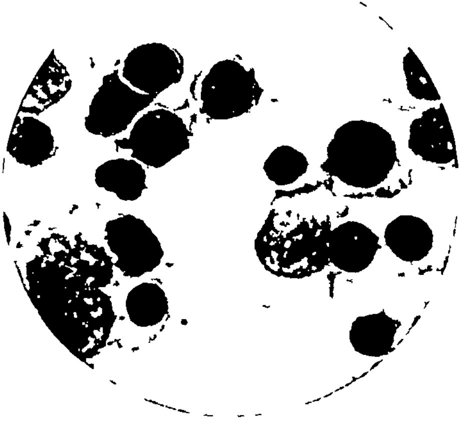

FIG 5

normoblasts, while quite numerous myelocytes and normoblasts were seen in the peripheral blood of Case 15 during the course of a superadded bronchopneumonia

Bone Marrow —Every case had at least one bone marrow examination carried out and all were megaloblastic before the commencement of treatment (Figs 2 and 3) The terminology employed is that of Israels [18, 19]

Repeat bone marrow examinations (Fig 4) were carried out in a number of cases in order to assess as early as possible response to treatment especially when the time available before the confinement was limited It has been clearly shown that the marrow exhibits the first detectable sign of response which is a change in the appearance of the megaloblastic nuclei, and precedes by a significant period of time changes in the reticulocyte and red cell level [20]

After a response had occurred as shown by reticulocytosis and more importantly by a rise in the red cell count, not every case was submitted to a further marrow examination, it being a reasonable inference that the marrow had reverted to the normal state However, a second sternal puncture was done in 6 cases (Nos 12, 13, 14, 16, 17, 18) and the bone marrow had reverted to the normoblastic state in all of these (Fig 5)

DIAGNOSIS

No case was accepted for this series unless the bone marrow was megaloblastic

Since it is clear that a macrocytic peripheral blood picture is by no means the rule, and in fact was present in only about one-third of the present series, it is obvious that many cases will be missed if this feature alone is relied upon for diagnosis Some cases have a frankly hypochromic blood picture The M C V may even be lower than the normal range It is for this reason that diagnostic difficulties occur, because simple iron deficiency anæmia is a relatively common blood disorder during and after pregnancy and it is obviously impracticable to examine the marrow of every anæmic pregnant woman Further, some of these simple iron deficiency anæmias may be remarkably resistant to oral treatment with iron [21] so the fact that iron therapy has failed is not certain evidence that some other ætiological factor is present It is advisable, however, to examine whenever possible the bone marrow of all pregnant women with an apparently refractory iron deficiency anæmia who have a red cell count of under 3½ mil One of the present series had a red count of 3½ mil , which is above the lower limit of the phsyiological anæmia of pregnancy according to some workers [22]

When the anæmia has been proved to be megaloblastic the diagnosis is still not established In all probability a pregnant or puerperal woman who has such a marrow suffers from the disease in question but some other possibilities exist Women with Addisonian pernicious anæmia may become pregnant, though this is rare [8, 23, 24] The finding of free hydrochloric acid in the gastric juice excludes this disease, but some cases of megaloblastic anæmia of pregnancy also show a histamine-fast achlorhydria Their final distinction from Addisonian pernicious anæmia must then depend on their ability to remain well without treatment, as shown by serial blood examinations carried out at intervals for two years Finally, other causes of megaloblastic anæmia must be borne in mind, for example a woman with the sprue syndrome (tropical sprue or idiopathic steatorrhœa) may become pregnant The distinction may usually be made on clinical and biochemical grounds Nutritional megaloblastic anæmia and its relationship to megaloblastic anæmia of pregnancy will be considered later

TREATMENT

Various forms of treatment were employed in the present series For convenience in assessment, cases are said to " respond " if a rise in the red cells and hæmoglobin follows treatment after a preliminary period of observation has revealed a stationary or falling blood level The reversion of the bone marrow from the megaloblastic to the normoblastic state is an essential part of the response As already stated this change was inferred in some cases from the degree of improvement in the peripheral blood In other cases, including any where doubt existed, the marrow change was proved by sternal puncture Cases which " respond " are subdivided into two groups, " satisfactory " where the red cell increase reaches or surpasses a certain chosen standard, and " unsatisfactory " where it fails to attain this standard The formula of Della Vida and Dyke [25] has been chosen for purposes of comparison

Refined Liver Extract—(Table V) Well known commercial extracts for parenteral administration were used and most of the batches employed had been tested for potency in cases of Addisonian anæmia Eleven cases in all were treated in this way Of the 5 treated with liver extract before delivery, none responded Of the 6 cases where treatment was instituted in the puerperium or immediately before delivery (Case 1) 3 failed to respond One response was " satisfactory," one " unsatisfactory " and one could not be assessed accurately owing to blood transfusion Thus the results of treatment with purified liver extract are in this series extremely poor This experience has been shared by others,[4, 6, 7, 12, 26, 27, 28] and contrasts with the results obtained in Addisonian pernicious anæmia In cases 2 and 4 it is possible that the quantity of liver extract used was insufficient to prove complete refractoriness to this treatment in the absence of bone marrow confirmation This quantity, however, would have produced a "satisfactory " response in Addisonian pernicious anæmia In case 5 which was treated during the puerperium, a satisfactory response might well have been obtained had a larger amount of liver extract been administered

Vitamin B_{12}—(Table V) There was no reason to suppose when vitamin B_{12} was isolated in 1948 [29 30] that it would be any more effective in the treatment of megaloblastic anæmia of pregnancy and the puerperium than refined liver extract Nor has this proved to be the case [12 31 32 33] Five of the present series were treated with B_{12} in doses varying from 10 µg to 120 µg Two cases were treated before and 3 after delivery There was no response in any of these cases

TABLE V

Results of Treatment with Refined Liver Extract and Vitamin B_{12} Cases are Divided into Two Groups according to whether Treatment was given before Delivery or After (*Case* 1 *is included in the latter Group*)

Case	Treatment Started		Treatment	Dosage	Duration	Average weekly rise in RBC during first 2 weeks of treatment mil /c mm	Expected Rise in RBC (Della Vida)	Response
	Before Delivery	After Delivery						
2	12 weeks		Refined liver ext	4 ml weekly	1 week	no rise		absent
4	14 days		ditto	4 ml weekly	1 week	no rise		absent
6	8 weeks		ditto	6 ml weekly	9 days	fall *		absent
9	3 weeks		ditto	4 ml weekly	3 weeks	no rise *		absent
13	years		ditto	1½ ml weekly	until 23rd wk of preg	fall *		absent
12	4½ weeks		B_{12}	10 µg in all	2 weeks	no rise		absent
15	6 days		B_{12}	40 µg in all	16 days	no rise *		absent
1	3 days		Refined liver ext	4 ml weekly	3 weeks	no rise		absent
5		14 weeks	ditto	1 ml in all	2 weeks	0 45	0 588	unsatisfactory
7		12 days	ditto	4 ml in all	2 weeks	no rise *		absent
8		8 weeks	ditto	4 ml weekly	3 weeks	cannot be assessed		present
10		2 weeks	ditto	6 ml weekly	1 week	fall *		absent
11		3 weeks	ditto	6 ml weekly	continuing	0 465	0 466	satisfactory
14		5 days	B_{12}	20 µg in all	2 weeks	no rise *		absent
16		3 days	B_{12}	120 µg in all	1 week	fall *		absent
18		2 weeks	B_{12}	80 µg in all	2 weeks	fall *		absent

* Sternal puncture performed at end of trial period (megaloblastic in each case)

Proteolysed Liver (Table VI) was given in 4 cases, 3 of which had failed to respond to refined liver Proteolysed liver was introduced in 1943 by Davis, Davidson, Riding and Shaw,[34] and is a papain digest of whole liver suitable for oral administration Two cases were treated before delivery and both responded although, in 1 the red cell increment was subnormal and the response, therefore, labelled " unsatisfactory " Two cases treated after delivery responded " satisfactorily " As will be seen these results are in every way comparable to those obtained with folic acid

Pteroylglutamic Acid—(Folic acid) (Table VI) was the method of treatment in 8 cases, 4 of which had failed to respond to B_{12} Doses varied between 10 mg and 45 mg daily A response occurred in every case Of 3 treated before delivery the response in 2 could not be assessed accurately on account of blood transfusion The third case (No 13) showed a "satisfactory" response

TABLE VI

Results of Treatment with Proteolysed Liver (P L) and Pteroylglutamic Acid (P G A) Cases are Divided into Two Groups as explained above, Table V

Case	Treatment Started		Treatment	Dosage	Average weekly rise in RBC during first 2 weeks of treatment mil /c mm	Expected weekly rise in RBC (Della Vida) mil /c mm	Response
	Before Delivery	After Delivery					
2	11 weeks		P L	40 gm daily	0 745	0 724	satisfactory
6	7 weeks		P L	40 gm daily	0 215	0 417	unsatisfactory
12	3 weeks		P G A	10 mgm daily	Blood transfusion prevents assessment		
13	17 weeks		P G A	30 mgm daily	0 675	0 552	satisfactory
17	4 weeks		P G A	30 mgm I M I	Blood transfusion prevents assessment		
3		1 week	P L	20 gm daily	0 60	0 509	satisfactory
4	5 days		P L	20 gm daily	Blood transfusion prevents assessment		
9		2 weeks	P G A	20 mgm daily	0 895	0 595	satisfactory
10		3 weeks	P G A	30 mgm I M I	0 690	0 466	satisfactory
14		3 weeks	P G A	20 mgm daily	0 110	0 442	unsatisfactory
15		10 days	P G A	45 mgm daily	0 595	0 517	satisfactory
16		8 days	P G A	20 mgm daily	0 185	0 564	unsatisfactory

Of 5 cases treated after delivery the response was "satisfactory" in 3 and "unsatisfactory" in 2 (Cases 14 and 16) One of these (Case 16) was seriously ill with an intercurrent infection while treatment was being given, and has already been referred to

Good results have in general been reported with folic acid [8, 31, 32, 33, 35, 36]

TABLE VII

Summary of Results of Treatment with Refined Liver Extract, Vitamin B_{12}, Proteolysed Liver, Pteroylglutamic Acid (P G A) and Citrovorum Factor

Treatment	Number of Cases Treated	Response	Failure
Refined liver extract	11	3	8
B_{12}	5	0	5
Proteolysed liver	4	4	0
P G A	8	8	0
Citrovorum factor	1	1	0

Case 18 was treated with Leuconostoc citrovorum factor[37] A "satisfactory" response was obtained Details of this and another case of megaloblastic anæmia of pregnancy, treated by the same substance, will be published shortly by Davidson and Girdwood * Citrovorum factor which is probably identical with folinic acid,[38, 39] is known to be active in Addisonian anæmia,[40] [41] but no report has yet appeared about its effectiveness in megaloblastic anæmia of pregnancy

A summary of the results of treatment is given in Table VII

Some of the cases, especially those showing an associated iron deficiency before the commencement of treatment, failed to continue to improve after an initial response until iron was also administered

PROGNOSIS

Before the introduction of proteolysed liver and folic acid, deaths frequently occurred Repeated blood transfusion was the main life-saving procedure

The outlook for the mother is now good provided the diagnosis is not so long delayed that labour ensues at a dangerously low blood level Every one of the present series made a complete recovery, although 2 (notably Case 16 already mentioned) were seriously ill for a time with intercurrent infections

Three women gave birth to still-born infants, but one of these was an anencephalic fœtus Of those babies born alive, including two sets of twins, all are now well except for one infant which died at the age of seven weeks of an unknown cause

FOLLOW-UP

A follow-up examination (Table VIII) of this series of cases was carried out In 2 cases (Nos 3 and 8) it was not found possible to get in touch with the individual concerned A further case (No 18) had been too recently treated to include in the follow-up investigation

Further Pregnancies had occurred in 3 patients (Cases 4, 7 and 10) Case 7 had 2 further pregnancies and although she was not seen by us during the first of these, the following information was obtained When apparently not more than two months pregnant she became anæmic No bone marrow investigation was carried out, but the Hb was 70 per cent and the R B C 2 64 M The film was macrocytic Folic acid was administered and the Hb rose to 92 per cent and the R B C to 4 7 M About this time she had an abortion From then until the time of her next pregnancy no treatment was given A healthy full-time child was born precisely one year later She was seen during the course of this pregnancy at the Blood Clinic and found to have a mild degree of iron deficiency anæmia, the R B C never falling below 4 3 M No folic acid was given

Case 10 was treated in another hospital When six months pregnant the Hb was 66 per cent and the R B C 2 9 M The blood film suggested macrocytosis No marrow examination was done but folic acid was administered with good clinical improvement The patient subsequently gave birth to a healthy full-time child

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* *Lancet* in Press

Thus there is reason to believe that 2 of the only 3 patients of the series known to have had subsequent pregnancies developed megaloblastic anæmia again Since one case had gone for two years and the other for two and a half years without treatment this development must be regarded as a true recurrence rather than a relapse in each case

Of the 12 patients who had not conceived again 6 had purposely avoided pregnancy

Hæmatological State

Erythrocyte Level—Every case had a red cell count of 4 3 M or higher, with the single exception of Case 12 Here the count was 3 78 M and a bone marrow examination was therefore carried out, this proved to be normoblastic Thus no patient showed any sign of a relapse to megaloblastic blood formation

Time without Treatment—Five patients had been without treatment for six years or longer, and a further 5 for one year or longer, the actual times being shown in Table VIII Four patients had gone for less than one year without treatment, since all 4 had had their megaloblastic anæmia less than one year before One patient (Case 11) had not stopped treatment owing to a misunderstanding

TABLE VIII

Details of Follow-up Investigation of 16 *Cases of Megaloblastic Anæmia of Pregnancy or the Puerperium*

Case	Time since Parturition	Further Pregnancy	Further Megalo blastic Anæmia of Pregnancy	Time since cessation of Treatment	Hb % & gm %	RBC mil /cmm	CI	MCV cμ	MCHC %	C N S
1	7½ years	0	0	7½ years	90 13 22	4 71	0 95	76 6	37 0	No abnormality
2	6½ years	0	0	6½ years	93 13 76	5 46	0 85	75 0	33 5	ditto
4	6 years	2	0	6 years	76 11 24	4 46	0 85			ditto
5	6½ years	0	0	6 years	98 14 5	4 78	1 03	78 4	38 6	ditto
6	6 years	0	0	6 years	96 14 2	4 78	1 0	83 6	35 5	ditto
7	5½ years	2	+	3 years	70 10 36	4 54	0 77	76 0	30 0	ditto
9	3½ years	0	0	3 years	83 12 28	4 33	0 96	83 1	34 1	ditto
10	3½ years	1	+	8 months	81 11 98	4 53	0 9			I S Q
11	2½ years	0	0	Treatment continues	90 13 32	5 00	0 9	77 0	34 6	No abnormality
12	2 years	0	0	2 years	73 10 8	3 78	0 96	71 4	40 0	ditto
13	1 year	0	0	1 year	96 14 2	4 65	1 03	94 6	32 2	ditto
14	1½ years	0	0	1½ years	79 11 69	5 04	0 78	79 3	29 2	ditto
15	1 year	0	0	7 months	95 14 06	4 83	0 98	84 8	34 2	ditto
16	7 months	0	0	5 months	98 14 5	5 95	0 82	67 2	36 2	ditto
17	3 months	0	0	3 months	87 12 87	4 46	0 97	96 4	29 9	ditto

Distinction from Addisonian Pernicious Anæmia—All 10 cases with free hydrochloric acid can be excluded Of the other 8, 4 have maintained a normal erythrocyte level without any treatment for two years or longer and may also be excluded Of the remaining 4, Case 10 had previously kept well for two years without treatment between her first and second attacks of megaloblastic anæmia of pregnancy and she has now been eight months without treatment following the latter Case 15 has kept well for seven months without treatment

Taking the whole series of 18 cases, therefore, Addisonian pernicious anæmia has not been finally excluded in 3 , Case 3 because nothing is known of her, Case 11 because treatment had not been stopped, and Case 15 because insufficient time has elapsed for a final decision to be reached

Nervous System—This was examined in 15 cases and no abnormality was detected except that the hemiparesis already noted in Case 10 was, of course, unchanged

General State—All 15 cases followed up were well, and general examination was negative except where otherwise stated

Iron Deficiency Anæmia—It will be observed that although the red cell level was satisfactory in all save Case 12 already mentioned, mild degrees of iron deficiency anæmia were common This is interesting in that many cases have a vague history of pallor, tiredness, etc , prior to pregnancy and that during pregnancy an associated iron deficiency is often found to accompany the megaloblastic anæmia Nevertheless, the 2 cases with the most marked hypochromic anæmia at follow-up (Cases 7 and 14) had little or no evidence of this during their pregnancy anæmia and neither of the 2 (Cases 6 and 9) with the most obvious associated iron deficiency during pregnancy, showed iron deficiency at follow-up There is thus no correlation in this respect amongst the present series of cases

DISCUSSION

At this point is may not be inappropriate to consider a much commoner disease similar to, or, as some [42] [43] think, identical with the megaloblastic anæmia of pregnancy and the puerperium seen in temperate zones Amongst the many names that have been applied to it are tropical macrocytic anæmia,[44] nutritional macrocytic anæmia,[45] and more recently nutritional megaloblastic anæmia [42] The disease, which has received careful study especially from Wills and her associates,[46–53] is a megaloblastic anæmia affecting pregnant and non-pregnant females and also males A similar anæmia has been described in Macedonia [45] and in Africa [54] Cord changes are not seen, free hydrochloric acid is often present and the age group is younger than in Addisonian pernicious anæmia [48] Wills found that the condition responded well to marmite, an autolysed yeast product [44] She found that dried yeast, watery extracts of yeast and preparations of vitamin B complex from other sources were inactive [53] Response to liver at first seemed satisfactory [48] but later it was found that refined liver extracts were often ineffective [55] As is the case with megaloblastic anæmia of pregnancy and the puerperium in this country there has been a lack of uniformity in the response of the disease to different forms of treatment

Thus Fairley and his associates[45] working in Macedonia, found that much larger quantities of marmite or crude liver might be required in their cases than in those seen in India Even then the blood level might improve only slowly There was a difference, too, amongst cases seen in India, Mudalier and Rao[56] for instance, getting no response to treatment with marmite Further, while Wills[55, 57, 58] and Watson and Castle[59] found refined liver extract ineffective, Moore and his colleagues[60] in the United States and Patel and Bhende[61] in India had a high measure of success using refined liver extract Vitamin B_{12} has also been found to be active in this same disease[62, 63, 64] The response to pteroylglutamic acid, however, seems to be uniformly satisfactory[65–69]

Watson and Castle[59] considered that the diversity of results following treatment suggested that more than one type of nutritional macrocytic anæmia might occur and that deficiency of a substance found in autolysed yeast which they suggested be called " Wills' factor " might be the cause of one Another type might be due to extrinsic factor deficiency The work of Day *et al*,[70] Wilson *et al*[71] and Furman *et al*[72] suggested that Wills' factor might be folic acid, but this view does not find general acceptance,[73, 74] Ungley[75] for instance, observing a response in a case of megaloblastic anæmia of pregnancy treated with an alcoholic extract of yeast containing less than 40 μg of folic acid per dose

Kothari and Bhende[43] feel that the evidence is overwhelmingly in favour of tropical macrocytic anæmia being essentially nutritional in origin and Bhende[42] accordingly suggests that the name nutritional megaloblastic anæmia be used Kothari and Bhende consider that there is no difference between this disease and the megaloblastic anæmia of pregnancy seen in temperate climates Pregnancy they suggest may precipitate a nutritional deficiency by increasing the requirements of a dietary factor present in " borderline " amounts Remission following pregnancy could also be explained along these lines

Certain objections may be made to regarding the two diseases as identical That seen in this country is never found to affect patients other than pregnant and recently pregnant women Pregnant women may develop it who have been taking a diet which appears to be beyond criticism, while others who have been taking a very bad diet may never succumb to the disease Evidence of faulty intestinal absorption as a possible factor in producing a conditioned nutritional deficiency has not been convincing Two of the present series of cases (Nos 9 and 17) with diarrhœa had a fat balance test[76] carried out which revealed no impairment of absorption, but it must be admitted that this method of examination may be unreliable The older theories as to causation of the disease—a hæmolytic agent,[2] a temporary deficiency of extrinsic factor[53] or intrinsic factor[77]—have had to be discarded, at least with regard to the ætiology of the majority of cases

Does the response of megaloblastic anæmia of pregnancy to various forms of therapy shed any light upon the ætiology ? Many kinds of treatement have been used, including whole liver,[6, 78] refined liver extract,[4, 5, 78] crude liver,[78] proteolysed liver,[80] hog's stomach,[4,79] yeast,[75] marmite,[78] B_{12},[31, 32 33] folic acid [8, 31, 32, 33, 35 36]

Amongst the most successful of these have been whole liver, proteolysed liver and folic acid The possibility naturally arises of folic acid being the factor common to these three Folic acid is present in whole liver and proteolysed liver, but virtually absent from refined liver extract Sufficient folic acid may be present in whole liver to account for its success, but in proteolysed liver the quantity present is of more doubtful significance [80] However, this possibility cannot be excluded Vilter and his associates [73] suggest that the active substance in proteolysed liver and some crude liver extracts is Wills' factor and that this is, as already stated, not folic acid These workers think that Wills' factor may function with folic acid in the synthesis of nucleic acid by activating the formation of purines and pyramidines, for example thymine, by methylation of uracil If this were the case, vitamin B_{12} would not be expected to be effective in a case of megaloblastic anæmia of pregnancy with a Wills' factor deficiency as it is believed to activate the formation of nucleosides such as thymidine from the purines and pyramidines already formed and so play an important part in a later stage of the synthesis of nucleic acid

Since, as far as can be known, folic acid is effective in all cases of megaloblastic anæmia of pregnancy and the puerperium in causing the bone marrow to revert to the normoblastic state and bringing about a rise in the blood level, and since folic acid in the form of its conjugates is a constituent of the normal diet, it is tempting to conclude that the disease is due to a deficiency of this substance Further, folic acid has been shown experimentally to be necessary during reproductive processes [81] and there is evidence of an increased requirement for this substance during pregnancy [82 83]

It is possible, however, that more than one type of deficiency occurs, in other words, as suggested by Thompson and Ungley,[12] that cases of megaloblastic anæmia of pregnancy and the puerperium do not form one homogeneous group

CONCLUSIONS

Although much remains to be discovered about the ætiology of megaloblastic anæmia of pregnancy, enough is known of the disease to permit certain conclusions of practical importance to be drawn

The disease is uncommon but probably less so than generally supposed

The importance to the mother and unborn child of early diagnosis and proper treatment cannot be over stressed

Many cases will be missed if a macrocytic anæmia is made the main criterion of diagnosis and no marrow examination is carried out

Folic acid is the treatment of choice, and is simple and effective It should be supplemented with iron

Treatment may be discontinued after the birth of the child when a normal blood level has been reached

Cases with a histamine-fast achlorhydria should be seen at intervals for two years after the cessation of treatment to exclude the possibility of their having Addisonian pernicious anæmia

The occurrence of megaloblastic anæmia during one pregnancy does not contraindicate another pregnancy provided adequate ante-natal care is available and the blood is examined at regular intervals

I wish to thank Professor Kellar, Dr Fahmy and Dr Douglas Miller for permission to refer to their cases and for access to obstetrical records I am grateful to Professor Davidson for advice and encouragement and to Miss S T Lindsay for the many blood counts involved

REFERENCES

[1] Channing, W (1842), *New Eng Quart Journ Med Surg*, 1, 157 [2] Osler, W (1919), *Brit Med Journ*, 1, 1 [3] Heilbrun, N (1936), *Journ Amer Med Assoc*, 107, 27 [4] Stevenson, E M K (1938), *Trans Edin Obstet Soc*, 58, 81 [5] Davidson, L S P, Davis, L J, and Innes, J (1942b), *Brit Med Journ*, 2, 31 [6] Fullerton, H W (1943), *Brit Med Journ*, 1, 158 [7] Callender, S T E (1944), *Quart Journ Med*, N S, 13, 75 [8] Davidson, L S P, Girdwood, R H, and Clark, J R (1948), *Brit Med Journ*, 1, 819 [9] Evans, W (1929), *Lancet*, 1, 14 [10] Boycott, J A (1936), *Lancet*, 1, 1165 [11] Reid, W J S, and Mackintosh, J M (1937a), *Lancet*, 1, 43 [12] Thompson, R B, and Ungley, C C (1951), *Quart Journ Med*, N S, 20, 187 [13] Davidson, L S P, and Davis, L J (1947), *Advances in Int Med*, 2, 481 [14] Osgood, E E (1935), *Arch Intern Med*, 56, 849 [15] Britton, C J C (1936), *N Z Med Journ*, 35, 154 [16] Wintrobe, M M (1932), *Journ Lab Clin Med*, 17, 899 [17] Whitby, L E H, and Britton, C J C (1950), *Disorders of the Blood*, sixth edition, London [18] Israels, M C G (1939), *Journ Path Bact*, 49, 231 [19] Israels, M C G (1941), *Lancet*, 2, 207 [20] Davidson, L S P, Davis, L J, and Innes, J (1942a), *Quart Journ Med*, N S, 11, 19 [21] Neary, E R (1946), *Amer Journ Med Sci*, 212, 76 [22] Adair, F L, Dieckmann, W J, and Grant, K (1936), *Amer Journ Obstet Gynec*, 32, 560 [23] Roberts, G F (1944), *St Barth Hosp Journ*, 48, 53 [24] Goodall, A (1940), *Lancet*, 1, 30 [25] Della Vida, B L, and Dyke, S C (1942), *Lancet*, 2, 275 [26] Goldenberg, H, and Wyatt, J P (1950), *Canad Med Assoc Journ*, 63, 289 [27] Eisenberg, S (1948), *Yale Journ Biol Med*, 21, 161 [28] Ginsberg, V, Watson, J, and Lichtman, H (1950), *Journ Lab Clin Med*, 36, 238 [29] Rickes, E L, Brink, N G, Koniuszy, F R, Wood, T R, and Folkers, K (1948a), *Science*, 107, 396 [30] Smith, E Lester, and Parker, L F J (1948), *Biochem Journ*, 43, Proc viii [31] Bethell, F H, Meyers, M C, and Neligh, R B (1948), *Journ Lab Clin Med*, 33, 1477 [32] Day, L. A, Hall, B E, and Pease, G L (1949), *Proc Staff Meet Mayo Clin*, 24, 149 [33] Ungley, C C, and Thompson, R B (1950), *Brit Med Journ*, 1, 919 [34] Davis, L J, Davidson, L S P, Riding, D, and Shaw, G E (1943), *Brit Med Journ*, 1, 655 [35] Moore, C V, Bierbaum, O S, Welch, A D, and Wright, L D (1945), *Journ Lab Clin Med*, 30, 1056 [36] Spies, T D (1946), *Journ Amer Med Assoc*, 130, 474 [37] Sauberlich, H E, and Baumann, C A (1948), *Journ Biol Chem*, 176, 165 [38] Bond, T J, Bardos, T J, Sibley, M, Shive, W (1949) *Journ Amer Chem Soc*, 71, 3852 [39] Shive, W, Bardos, T J, Bond, T J, and Rogers, L L (1950), *Journ Amer Chem Soc*, 72, 2817 [40] Spies, T D, Lopez, G G, Milanes, F, Toca, R L, Roberedo, A, and Stone, R E (1950), *Sou Med Journ*, 43, 1076 [41] Davidson, L S P, and Girdwood, R H (1951), *Lancet*, 1, 722 [42] Bhende, Y M (1949), *Indian Journ Med Sci*, 3, 131 and 211

[43] Kothari, B V , and Bhende, Y M (1949), *Indian Journ Med Res* , 37, 347 [44] Wills, L (1931), *Brit Med Journ* , 1, 1059 [45] Fairley, N H , Bromfield R J , Foy, H , and Kondi, A (1938), *Trans Roy Soc Trop Med Hyg* , 32, 132 [46] Balfour, M I (1927), *Indian Med Gaz* , 62, 491 [47] McSwiney, S A (1927), *Ibid* , 62, 487 [48] Wills, L , and Mehta, M M (1930a), *Indian Journ Med Res* , 17, 777 [49] Wills, L , and Mehta, M M (1930b), *Ibid* , 18, 307 [50] Wills, L , and Mehta, M M (1930c), *Ibid* , 18, 663 [51] Wills, L , and Talpade, S N (1930), *Ibid* , 18, 283 [52] Wills, L , and Bilimoria, H S (1932), *Ibid* , 20, 391 [53] Wills, L , (1934), *Ibid* , 21, 669 [54] Trowell, H C (1943), *Trans Roy Soc Trop Med Hyg* , 37, 19 [55] Wills, L , and Evans, B D F (1938), *Lancet*, 2, 416 [56] Mudaliar, A L , and Rao, K N (1932), *Indian Journ Med Res* , 20, 435 [57] Wills, L , Clutterbuck, P W , and Evans, B D F (1937), *Lancet*, 1, 311 [58] Wills, L (1948), *Blood*, 3, 36 [59] Watson, J , and Castle, W B (1946), *Amer Journ Med Sci* , 211, 513 [60] Moore, C V , Vilter, R , Minnich, V , and Spies, T D (1944), *Journ Lab Clin Med* , 29, 1226 [61] Patel, J C , and Bhende, Y M (1949), *Blood*, 4, 259 [62] Patel, J C (1948), *Brit Med Journ* , 2, 934 [63] Patel, J C , and Kocher, B R (1950), *Brit Med Journ* , 1, 924 [64] Chaudhuri, S (1951), *Brit Med Journ* , 2, 825 [65] Das Gupta, C R , and Chatterjea, J B (1946), *Indian Med Gaz* , 81, 402 [66] Kemp, T A (1947), *Lancet*, 2, 350 [67] Goodall, J W D , Goodall, H I , and Banerjee, D (1948), *Lancet*, 1, 20 [68] Spies, T D , Lopez, G G , Stone, R E , Milanes, F , Toca, R L , and Aramburu, T (1948), *Lancet*, 1, 239 [69] Ramalingaswami, V , and Menon, P S (1949), *Indian Journ Med Res* , 37, 471 [70] Day, P L , Mims, V , Trotter, J R , Stokstad, E L R , Hutchings, B L , and Sloane, N H (1945), *Journ Biol Chem* , 157, 423 [71] Wilson, H E , Saslaw, S , and Doan, C A (1946), *Journ Lab Clin Med* , 31, 631 [72] Furman, R H , Daniels, W B , Jr , Hefner, L L , Jones, E , and Darhy, W J (1950), *Amer Pract* , 1, 146 [73] Vilter, R W , Horrigan, D , Muellar, J F , Jarrold, T , Vilter, C F , Hawkins, V , and Seaman, A (1950), *Blood*, 5, 695 [74] Smith, E Lester (1950), *Journ Pharm Pharmacol* , 2, 409 [75] Ungley, C C (1950), *Ibid* , 2, 540 [76] Cooke, W T , Elkes, J J , Fraser, A C , Parkes, J , Peeney, A L P , Sammons, H G , and Thomas, G (1946), *Quart Journ Med* , 15, 141 [77] Strauss, M B , and Castle, W B (1933), *Amer Journ Med Sci* , 185, 539 [78] Miller, H G , and Studdert, T C (1942), *Lancet*, 2, 332 [79] Wilkinson, J F (1932), *Journ Obstet Gynæc Brit Emp* , 39, 293 [80] Davidson, L S P (1948), *Blood*, 3, 107 [81] Thiersch, J B , and Philips, F S (1950), *Proc Soc Exper Biol Med* , 74, 204 [82] Sica, A J , Allgeier, A M , and Cerecedo, L R (1948), *Arch Biochem* , 18, 119 [83] Spies, T D (1949), *Surg Gynec Obst* , 89, 76

OBITUARY

EDWIN BRAMWELL, M D, C M, F R C P Lond & Edin, LL D Edin, Hon M D Melb, F R S E

PROFESSOR BRAMWELL died in Edinburgh on 21st March after a long and painful illness

He was the eldest son of Sir Byrom Bramwell, M D, F R C P E, LL D, and was born in North Shields in 1873 His early education was at Cheltenham, and from there he entered the University of Edinburgh to study Medicine After qualifying in 1896 he became resident physician to Professor Grainger Stewart in the Royal Infirmary and at the same time was elected one of the Presidents of the Royal Medical Society A period of continental travel was common in these days, and Bramwell followed the fashion by studying for a time at Frankfurt, Freiberg, Heidelberg and Paris On returning to Britain in 1899 he acted as Resident Medical Officer at Queen Square Hospital for Nervous Diseases The following year he took the Membership of both the Edinburgh and the London Colleges of Physicians After his return to Edinburgh his first appointment was as Assistant Physician to Leith Hospital in 1902, and in 1907 he was elected Assistant Physician to the Royal Infirmary

Post-graduate education in Medicine always interested him deeply He became secretary to the joint committee appointed by the University and the Royal Colleges to arrange and supervise post-graduate courses Later he acted as chairman of this committee His enthusiasm and his painstaking work on behalf of the committee made a success of the scheme, and to him more than to any other individual is due the reputation and high standard of the post-graduate courses in Edinburgh

Edwin Bramwell qualified as an extra-mural lecturer in medicine and for a number of years was associated with his father in running a highy successful course in systematic medicine

During the war of 1914-18 he was mobilised as a Captain in the second Scottish General Hospital at Craigleith (now the Western General) and the Royal Victoria Hospital Here he acted as physician and neurologist and was in charge of those who suffered from shell shock When the War Office set up a committee to inquire into shell shock and advise the Army on such cases Bramwell was invited to become a member

In 1919 he was promoted to full charge of Medical Wards in the Royal Infirmary He soon attracted a large clinic for nervous cases and became recognised as a reliable and helpful consultant The University appointed him lecturer in Clinical Neurology and he gave regular courses of lecture demonstrations which, though voluntary, attracted large numbers of under graduates His work in the wards was of a very high standard and he was an excellent teacher He was always courteous towards his patients, even the most stupid and trying, and never caused them embarrassment before the students His success with neurotic or hysterical cases was often dramatic, and his careful handling of patients must have impressed many generations of students From his assistants he demanded the highest standards of medical

EDWIN BRAMWELL

work and he instilled into them a full sense of the responsibilities of the profession and a feeling that nothing but the best was acceptable

When Professor Darby Boyd died prematurely in 1922, Edwin Bramwell was selected to succeed him in the Moncrieff Arnott Chair of Clinical Medicine This appointment included the chairmanship of the Clinical Medicine Board, and his tact and charm carried the Board successfully through difficult times He continued his interest in neurology, and his voluntary lecture-demonstrations attracted large numbers of students and post-graduates After fifteen years in charge of wards he resigned his chair in 1934 and was appointed Consulting Physician

Professor Bramwell was well known outside Edinburgh and he was recognised as one of the leading neurologists in Britain Many honours came to him He was invited to deliver the Morison Lectures of the Royal College of Physicians of Edinburgh (1916 and 1917), the Bradshaw Lecture (1925) and the Croonian Lecture (1937) of the College of Physicians of London During a tour of Australia in 1935 he gave the Halford Oration at Canberra and was made an honorary M D of Melbourne The University of Edinburgh gave him the degree of LL D in 1937 He was President of the Royal College of Physicians of Edinburgh during the years 1934 and 1935 An original member of the Association of Physicians he was invited to become a corresponding member of the Neurological Societies of Paris and Philadelphia and at various times he was president of the Association of British Neurologists, the Neurological Section of the Royal Society of Medicine and of the Section of Neurology of the B M A (1927 and 1935)

Professor Bramwell was a first-class clinician, a close and patient observer and a prolific writer His painstaking and extensive study of encephalitis lethargica gained him the degree of M D in 1919

He was happy in his home life His wife, the elder daughter of Professor J D Cunningham, was a loyal support, a charming hostess and a devoted nurse To her and to his son and daughters we extend our deepest sympathy, and we mourn the passing of a charming personality and a much beloved colleague

NEW BOOKS

Brain Metabolism and Cerebral Disorders By HAROLD E HEMWICH, M D Pp 452, with 52 illustrations London Baillière, Tindall & Cox 1951 Price 46s 6d

This book might be described by a clinician as complementary to the study of neurology, in that it explains the ancillary sciences, the description being essentially, as indeed the title suggests, from the viewpoint of physiology and biochemistry Perhaps, regretfully, these aspects have become increasingly important in modern conditions, yet it is with a sense of nostalgia that the physician surrenders what he regarded as a sharpened wit to the laboratory worker whose life is spent under so much more static a condition

Saying this must in no way detract from the importance and usefulness of this study Here the normal cerebral mechanism is computed and the variations wrought in this rate by anoxia, narcosis and such diseases as psychosis, mental deficiency and avitaminosis are estimated These studies are of great practical interest to the clinician for whom they clarify the effect on the brain of anæsthesia and various therapeutic measures

We should all try to understand the levels of function if we are to interpret properly the dysfunction which confronts us A study of this book is a great help

Ophthalmology By ARNO E TOWN, M D Pp 511, with 208 illustrations and 4 coloured plates London Henry Kimpton 1951 Price 70s net

In the post-war years so many textbooks of ophthalmology have been produced that another is viewed with some critical interest Professor Town's book is written for the undergraduate and the general practitioner and some sections have been contributed by colleagues

The book includes sections on anatomy and physiology, optics, neuro-ophthalmology and medical ophthalmology and has interesting chapters on therapy and on " Standing Orders for Industrial Dispensaries "

Some aspects of ophthalmology are dealt with in considerable detail and the photographs and illustrations are outstandingly good The section on glaucoma is disappointing The early symptoms of this disease are of great importance to the general practitioner and, as the basis of the conduct of a case of glaucoma lies largely in the observation of the visual fields, this aspect could, with benefit, have received more space

The book is thoroughly up to date in pathology and in treatment, and to the British reader the contemporary American view on ophthalmology is of interest

A Synopsis of Ophthalmology By J L C MARTIN-DOYLE, M R C S, L R C P, D O (OXON) Pp 246 Bristol John Wright & Sons 1951 Price 20s

This *Synopsis of Ophthalmology* is contained in a book of pocket size and is designed to meet the needs of the undergraduate, the general practitioner and the ophthalmic house surgeon working for a higher diploma in ophthalmology The author has managed to include an amazing amount of information in little bulk and the references to recent work in ophthalmology serve to keep the general practitioner abreast of progress in the specialty Not everyone will agree with many of the views held, but for its size this must be one of the best books of its type

NEW EDITIONS

A Textbook of Medicine By RUSSELL L CECIL and ROBERT F LOEB Eighth Edition Pp xxxi+1627, with 204 figures and 40 tables London W B Saunders 1951 Price 60s

Textbooks in medicine are too numerous and some are too long and others too short, but this is a well laid out work covering every branch of internal medicine Balance is maintained between competing interests, and it is obvious that all the contributors have worked loyally and co operatively to a well thought out plan No subject overrides the others There are no unnecessarily long introductions nor weary tables of statistics but in each article the writer gets down to his subject and produces a clear and attractive account, which is complete and up to date At the end of the article is a short list of references, mostly American In spite of its many authors this is a well written book, more than adequate for students and suitable for post-graduates The illustrations are of real value The book is easy for reference

Aids to Physiology By H DRYERRE, PH D, M R C S, M R C P, F R S E Fourth Edition Pp vii+327 London Baillère, Tindall & Cox 1951 Price 7s 6d net

A new edition of this small book has been produced after a lapse of nine years Considerable alterations have been made to include the advances made in the interval, specially in biochemistry It continues to act as a synopsis to supplement the standard textbooks

Fractures and Joint Injuries By SIR REGINALD WATSON-JONES, B SC, M CH ORTH, F R C S, F R C A S, F A C S Fourth Edition In two volumes Vol I—Pp 470, with 709 illustrations Edinburgh E & S Livingstone Price (for two volumes) £6

The fourth edition of this world famous textbook has now started publication, the first volume being already on sale Though the original format has been preserved little else has, since every chapter has been rewritten and many new ones added, along with some two hundred more illustrations The new chapters include those on wound shock, the treatment of open fractures, control of infection, and a review of bone diseases that covers almost the whole of orthopædic surgery It will be seen that it overflows from the remit of its title, and no doubt Sir Reginald will develop his textbook till it really does contain everything an orthopædic surgeon must know One of the most interesting bits is the vigorous attack that is made on the belief that contact compression promotes union of fractures We have always relied on the Liverpool School of Orthopædic Surgery to do its share of debunking and are glad to know that this valuable faculty has been carried in the luggage to London The various chapters are of such a uniformly high standard that it is invidious to select any for special mention Transplantation of bone, with its wealth of beautiful illustrations, is particularly good and complete Like other chapters it is the more interesting because of the historical background of the subject—much of it, one is proud to say, in Scotland A happy change in this first volume is the inclusion of an index which, in previous editions, was only in the second volume

The book is most beautifully produced, many of the illustrations being in colour, the first two, of H O Thomas and Sir Robert Jones, being delightfully reminiscent of the author's own consulting room The volume is well up to the high standard expected from such an author and from such publishers It is to be noted that the two volumes are not sold separately, but as a set, but who would want to buy only one!

BOOKS RECEIVED

The American Rheumatism Association Rheumatic Diseases (*W B Saunders Company, London*)	60s
BEAUMONT, G E, M A, D M (OXON), F R C P, D P H (LOND), and DODDS, E C, M V O, D SC, PH D, M D, F R C P, F R I C, F R S (EDIN), F R S Recent Advances in Medicine Thirteenth Edition (*J & A Churchill Ltd, London*)	27s 6d
BLAND, JOHN H, M D The Clinical Use of Fluid and Electrolyte (*W B Saunders Company*)	32s 6d
CAMERON, GORDON ROY, M B, D SC (MELB), F R C P, F R S Pathology of the Cell (*Oliver & Boyd Ltd, Edinburgh*)	£4, 4s net
Edited by CONN, HOWARD F, M D Current Therapy, 1952 (*W B Saunders Company, London*)	55s
CONYBEARE, Sir JOHN, K B E, M C, D M (OXON), F R C P, and MANN, W N, M D (LOND), F R C P Textbook of Medicine Tenth Edition (*E & S Livingstone Ltd, Edinburgh*)	37s 6d net
Edited by DALEY, RAYMOND, M A, M D CAMB, M R C P, and MILLER, HENRY, M D DURH, M R C P, D P M Progress in Clinical Medicine Second Edition (*J & A Churchill Ltd, London*)	30s net
FROHSE, FRANZ and BRODEL, MAX Atlas of Human Anatomy (*George Allen & Unwin Ltd, London*)	16s net
GIRDLESTONE, G R, and SOMERVILLE, S W, M B, F R C S (ED) Tuberculosis of Bone and Joint Second Edition (*Oxford University Press, Toronto, Canada*)	45s net
GLIDDEN, PAUL, and POWELL, MURIEL B Called to Serve (*Hodder and Stoughton, London*)	7s 6d net
GRISHMAN, ARTHUR, M D, and SCHERLIS, LEONARD, M D Spatial Vectorcardiography (*W B Saunders Company, London*)	30s
HOWORTH, M BECKETT, M D A Textbook of Orthopedics (*W B Saunders Company, London*)	80s
ISCHLONDSKY, N E, M D Brain Mechanisms in Coronary Disease (*Henry Kimpton, London*)	25s net
JOHNSTONE, R W, C B E, LL D, M A, M D, F R C S E, M R C P E, F R C O G, F R S E A Textbook of Midwifery Fifteenth Edition (*Adam & Charles Black, London*)	30s net
JORDAN, EDWIN P, M D, and SHEPARD, WILLARD C ℞ for Medical Writing (*W B Saunders Company, London*)	12s 6d
KLEINBERG, SAMUEL, M D Scoliosis Pathology, Etiology and Treatment (*Baillière, Tindall & Cox, London*)	57s 6d net
MASTER, ARTHUR M, M D, MOSER, MARVIN, M D, and JAFFE, HARRY L, M D Cardiac Emergencies and Heart Failure (*Henry Kimpton, London*)	22s net
MOYER, CARL A, M D Fluid Balance (*The Year Book Publishers Inc, Chicago, U S A*)	$3 75
Edited by OGILVIE, Sir HENEAGE, K B E, D M, M CH, F R C S, and THOMSON, WILLIAM A R, M D Practical Procedures Second Edition (*Eyre & Spottiswoode, London*)	25s net
PARMELEE, ARTHUR HAWLEY, M D Management of the Newborn (*The Year Book Publishers, Inc*)	$7 00
PINEY, A, M D, F R C P A Clinical Atlas of Blood Diseases Seventh Edition (*J & A Churchill Ltd, London*)	21s net
PORTMANN, GEORGES, M D Diseases of the Ear, Nose and Throat (*The Williams & Wilkins Company, Baltimore, U S A*)	£7, 10s net
RODDIS, LOUIS H James Lind (*Wm Heinemann, London*)	21s net
WATTS, C A H, M D (DURH), D OBST R C O G, and WATTS, B M, M B, B S (DURH) Psychiatry in General Practice (*J & A Churchill Ltd, London*)	12s 6d
WHITE, FRANK D, A R T C, PH D (EDIN), F R I C, and DELORY, GEORGE E, M SC, PH D (LOND) A Course in Practical Biochemistry Sixth Edition (*J & A Churchill Ltd, London*)	17s 6d net

Edinburgh Medical Journal

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REFLECTIONS FROM A PROVINCIAL DEANERY

By J G McCRIE, O B E , T D , M B , F R C P E

Dean of the Faculty of Medicine, University of Sheffield

I THINK I need scarcely emphasise the honour which I feel it to have been invited to deliver a Honyman Gillespie lecture In one respect I at first fancied myself to be more fortunate than some of the other speakers in the series must have been, for I thought that at least I should not find it difficult to avoid reference to the subject of animal experimentation He would, I felt, be an ingenious man who, in exploring the subject with which I propose mainly to deal—namely, some aspects of Medical School administration—could devise a series of laboratory procedures designed to throw light on the problems connected therewith, intriguing and difficult though some of these problems undoubtedly are Then it struck me that one of the reasons for my venturing to address you this evening at all is that I am somewhat in the position of being able to report upon an experiment To explain myself, may I say that I wish first to offer some observations upon the nature of, and the functions attaching to, the Deanship of a Faculty of Medicine, with particular reference to the question of whether it is desirable, or undesirable, for such a Dean to be a full-time officer Since the University of Sheffield was the first, and I think still remains the only, undergraduate Medical School both to decide upon such an appointment and to fill it with one who was previously a stranger to the School, I feel it is not incorrect to speak, in this connection, of an experiment I hope I do not seem to be striking too personal a note If I do, I can only plead that this seems to me to be, putting all personal questions aside, quite an important matter upon which those with an interest in medical administration may possibly find it useful to hear something, in relation to a policy whose desirability or otherwise is still the subject of quite widespread discussion I shall try to be as objective as possible , and I should like to emphasise this point, since otherwise it might be thought that some of what I have to say was intended as criticism with a personal tinge This is far from being the case I am deeply appreciative of the way in which I, a newcomer into a post of a new type, have been received by my colleagues It may be—it would be strange if it were not—that some of them hold views, which are different from my views, as to what constitutes the best and most convenient type of medical school administration, but I have never been conscious that this tinged their personal attitude

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A Honyman Gillespie Lecture delivered in Edinburgh, on Thursday, 14th December 1950 towards myself, and I trust I shall be believed when I say that the converse is—or at least that I earnestly try to make it—also true

The Goodenough Committee (1944) gave it as their opinion that " in most, possibly all, medical schools, it will soon become advantageous, if it is not already so, for the office of dean to be a whole-time (or almost whole-time) appointment " The reasons underlying this opinion—whether it be right or wrong—are not far to seek It has hitherto been the custom—and here one is speaking of University Faculties of Medicine, for such is not necessarily true of all Faculties in all Universities—for the holder of the office of Dean to be also a Professor, and, as such, the head of an important University Department It has also been usual—and here again we note a difference from other Faculties, especially in the English Provincial Universities—for the same person to hold the office over a considerable period of years I fancy most of us will think this sensible , and the Goodenough Committee " felt it to be open to question whether too frequent changes in the office of dean are in the best interests of a medical school " Since full-time clinical chairs are of comparatively recent development, it follows that the Dean has in the past usually been the head of a large non-clinical department (The Deans of the London Medical Schools are in a somewhat different case They are, of course, officers of their own Medical Schools, not officers of the University , consequently their time is chiefly devoted to School affairs, and they are, generally speaking, not greatly involved in general University matters The whole problem is somewhat different—(it is presumably because of this that the Deans of the London Schools are frequently practising clinicians)—and it is not proposed to deal further with it here In what follows I have in mind chiefly the Dean of a University Faculty of Medicine, as seen typically in the English Provinces and in Scotland) The amount of work which such a Dean must undertake has undergone an enormous increase of recent years Even the problem of student-selection alone has vastly increased In my own School, up to 1939, the applications for admission roughly balanced the number of places available, and the chief task in selection was to discourage the relatively small number of applicants who were clearly unsuitable Now we have, for each place, at least five applicants who must be seriously considered, apart altogether from the number who can be turned down on their paper applications While a large part of the work in this connection is clerical, and can be dealt with by enlarging sufficiently the Dean's office staff, a not inconsiderable part of the burden must be shouldered by the Dean himself The National Health Service Act, too, has added to his responsibilities It is true that, in pre-N H S days, the Dean was frequently a member of the governing body of the teaching hospitals associated with his University, but the new Act, both explicitly and by implication, makes it necessary for University representatives to play an even larger part in hospital affairs, and the Dean of the Faculty of Medicine is a fairly obvious choice for membership not only of the appropriate Regional Hospital Board and (in England) Board of Governors of the Teaching Hospital, but also of many of the Boards' most important committees Nor does general University administration become any simpler Staffs are larger, therefore there are more new appointments to be made, promotions to be considered, etc Budgets reach astronomical figures, and require more time-consuming preparation In all of these general University matters, it is to be presumed that, if the Faculty of Medicine is to be properly regarded within the University, the Dean of that Faculty must play his part And, of course, the business of his own Faculty shares in the increased complexity Apart from the general matters just referred to, new legislation brings new responsibilities The assessing of house-posts as to their suitability for the period of internship prescribed by the new Medical Act will be a big initial task, and the collection of reports as to how the internships are performed, and the issuing of the necessary certificates, a permanent and continuing one Then there is the whole problem of post-graduate education—from the operation of suitable schemes for the appointment and training of registrars, through the arranging of specialised diploma and other courses, to the working out and provision of the best types of instruction for general practitioners

It will be admitted that this sort of burden is not one that can be carried over a long period by one individual, and yet leave him much time (even if it be in a supervisory rather than a personal capacity) for the teaching and research which are the prime duties of the Professorial Head of a University Department Either, except in the case of an individual of exceptional gifts, he will have insufficient time to devote, personally, to his duties as Dean, or his departmental work—and probably in the first instance his research—will suffer It seems a simple solution to say that in future Deans should be appointed as whole-time officers Of course this *is* one solution, but I feel it worth while to glance at some of the disadvantages associated with it , and it may be convenient at the same time to suggest possible methods by which these disadvantages may be avoided or lessened

Presumably the first disadvantage that may be felt to attach to a full-time Dean is that he is less easily got rid of than is one subject to periodic election—for I suppose it may be presumed that, once a full-time officer of the University is appointed, he is appointed *ad senectutem aut ad culpam* With this goes the fear, on the part of those who distrust the idea of full-time Deanships, that the person appointed may forget the scriptural injunction " whosoever will be chief among you, let him be your servant," and may seek to make himself into a manager or dictator This possibility is of course difficult to insure against, except by taking care over the appointment initially and by continuing vigilance on the part of the Dean's colleagues It may, however, be noted that, while in many Universities the Dean is automatically regarded as Chairman of the Faculty Board, this is not so in all The *Oxford Dictionary* defines a Dean as a "President of a Faculty," and I think he is pretty generally accepted as such, in so far as his position in the general University hierarchy is concerned But it does not follow that he is also Chairman of the Faculty Board, *i e* that he is in the Chair at what may be called business meetings It is clear that, *if this is not so, the opportunities for the Dean to force* his opinions on the meeting are less It would appear from such discussions as I have had with others—and these others comprise representatives of most of the English Provincial Universities—that each body thinks its own practice the best, some Faculties would never think of having the Dean in the Chair, others would regard anything else as impracticable I mention the point because it does suggest a method of preventing a full-time Dean from becoming too assertive, and it is a method of procedure which many experienced University administrators say they find to work well in practice Others, it must equally be emphasised, are against it on grounds either of general principle or of increased administrative complexity I share this latter view, since I think that to have, as Chairman of the Faculty Board, someone other than the Dean suggests the use of the word "Dean" in the sense in which it is used in some (though not all) American Schools, *i e* that of "secretary" rather than "president" I should add that I speak with no sense of personal rancour, since, although in my own University we have now established the office of Chairman of the Faculty Board on an elective basis, as distinct from the full-time Deanship of the Faculty, my colleagues have done me the honour, in each of the last three years, of electing me to the Chairmanship in question

My next point is a little more delicate I presume that, when the Deanship is on an elective basis, the choice is usually made because of supposedly special gifts of administration and leadership in the person elected But of course the choice is from among persons who have all already achieved the high degree of academic distinction or scientific prowess associated with occupancy of a Professorial Chair, and it is a question whether such distinction or prowess is not a *sine qua non* in one who aspires to be a Dean in the full sense referred to above—not only from the point of view of intra-Faculty relationships, but also having regard to the position which a Dean must occupy in the University as a whole, as, for instance, a member of the Senate If so, the choice of candidates suitable for appointment to a full-time Deanship is obviously severely limited, since few teachers or researchers *at the height of their powers would wish to retire* from that particular field There appear to be two solutions to the problem—to find a man of proved academic achievement who nevertheless, for some adequate reason, is desirous of transfer to the different, though not necessarily less exacting or interesting, field of administration, or, if making a selection from among candidates with a different background, to make that selection very carefully, and to be quite firm in the decision to make no appointment if no applicant considered to be of a suitable type presents himself

Another difficulty which is likely to arise when a non-Professorial Dean is appointed is a highly practical one, and that is the difficulty of his maintaining adequate contact with the student body I use the word "adequate" deliberately, because the question is not one purely of degree It is qualitative as well as quantitative The student, naturally, regards the teacher whom he meets in the lecture theatre, the dissecting room, the morbid anatomy laboratory, or the hospital ward, with an affection and respect which is captured only with difficulty by the man who (the student thinks) does nothing but sit all day in an office And of course the matter is quantitative as well , the full-time Dean just has not the physical opportunity to meet many students frequently And yet his role in this respect, at any rate in the smaller Schools, has always been one of great importance, and I need not enlarge on its obvious potentialities in relation both to present morale and to the help he ought to be able to continue to extend to former students in their after-careers This indeed is one of the great difficulties of the full-time Deanship If the latter has become necessary because of the increase of administrative duties, it is this press of administrative work which itself renders contact with students so difficult There is of course no solution which meets every case, but broadly speaking a remedy can be sought along two main lines (i) by giving to the full-time Dean some small share in teaching work, and (ii) by the Dean himself doing all in his power to make contact with the undergraduate body through all other available channels Under the first head, I do not feel that the instruction given by a full-time Dean can be in any of the main subjects, clinical or pre-clinical He cannot possibly keep sufficiently up to date with these for him to feel any pride or confidence in the instruction he gives Any form of "doctoring" is a 100 per cent job, not a 10 per cent one But there are, I think, certain subjects which offer possibilities, *e g* the philosophic background to medicine (if the Dean's tastes and gifts lie in that direction), the history of the local Medical School (or Medical History in general, if he knows enough about it), medical ethics (if he has ever been a practising doctor), and so on Under the second head, again personal tastes come in I recently asked a very distinguished London Dean what the answer to this problem was He replied that it was to be found on the football field Since I myself intensely dislike any form of violent exertion, I cannot apply his remedy literally , but, as Sam Weller remarked, "hooroar for the principle" It is certainly most important for a full-time Dean not only deliberately to set aside regular times for the periodic interviewing of all his students, but also to be available when required for consultation on special problems, to take the Chair at student meetings, and generally to seek to make himself regarded as one interested in, and capable of playing a useful part in, undergraduate affairs

The fact that I have devoted so much time to discussing the various ways in which the disadvantages of a full-time Deanship can be got over perhaps serves to emphasise that these disadvantages do in fact exist—which leads one to a consideration of the problem of whether the needs to which a full-time Deanship is one answer can be met in any other way One obvious possibility, which has been the solution adopted by several Medical Schools for a number of years, is to put the day-to day control of the Faculty Office under a Secretary or Senior Administrative Officer who is himself a medical man There is no doubt that in this way a considerable burden can be lifted from the Dean's shoulders, for a great deal of the routine work can quite properly be undertaken by a Medical Secretary At the decanal level itself, too, more sharing of duties than has been customary in the past is quite practicable One obvious division, which in fact has already been made in many Schools, is to separate undergraduate from post-graduate affairs and to have both an " Undergraduate " Dean (who, by custom, still seems usually to be referred to as " the Dean ") and a Post-graduate Dean or Director There can be further sub-divisions within these spheres, as for instance when the (Undergraduate) Dean is supported by a Clinical Sub-Dean, whose sphere is implicit in his title, and sometimes by an Academic Sub-Dean as well In the absence of a full-time Dean, such sub-divisions are necessary, for, even with a large part of the routine office work taken off the Dean's shoulders by a Medical Secretary, supported by an adequate clerical staff, there still remain a multitude of other duties which can properly be performed only by one who ranks as an Academic Officer rather than as a purely administrative official One has in mind, for instance, the representation of the Faculty, or of the University itself, on important outside bodies and committees, where the representative may require to speak with more authority than would be possible in the case of the holder of a purely executive office

It is really not my purpose to-night to recommend any particular procedure as the best Obviously, different places and different circumstances call for different measures I happen now to belong to a University where one particular policy has been adopted, and it is clearly for others, rather than for myself, to say whether or not it has been a success I do, however, feel that *it* may be useful to those who may have to consider this problem in other places or at other times to hear something of the question as viewed from one particular angle I think quite a good case can be argued that, for various reasons which have been indicated above—and doubtless for others also—it is wise to retain the old idea of a part-time Deanship on an elective basis In this case, a good deal of devolution will be required even at what may be called the " policy " level, and the various duties which it has in the past been customary for the Dean to undertake in person will have to be shared among an *increasing* number of his colleagues In addition, the routine administrative side will require considerable strengthening, this including (where such an arrangement does not exist already) putting the office side in the charge of a medically qualified individual who will undertake much of what were formerly regarded as decanal duties, such as the interviewing of prospective students and their parents, disciplinary work except in really severe cases, and so on I may say that, from some personal experience, I regard this arrangement as not at all a bad one It preserves many of the advantages of the old system, and avoids some of the difficulties of the new It is true that I personally would prefer to be a Dean than to be a Medical Secretary, and that fortune has favoured me in enabling me to undergo such a metamorphosis, but, looking at the question objectively, I can see many advantages in the system just outlined On the other hand, " it's an ill bird that fyles its ain nest," and I certainly do not want to be understood as condemning the alternative system—the full-time Deanship It has many administrative conveniences, it fits well into modern University and hospital organisation, and, always given the necessary compatibilities of personality, it can be made to work satisfactorily I should naturally hesitate to say—because it is clearly for others, and not for me, to make the judgment—that that has been proved in my own School, but there are after all other Schools that have made comparable experiments and apparently found them satisfactory I feel that I have discharged my duty in this respect to-night if I merely sketch the possibilities, and leave it to others to make the choice between them I do feel, however, that it is important for any School considering the possibility of appointing a full-time Dean to make up its mind fully that this is genuinely what it means, and that it does not have the intention of merely giving an imposing title to someone whom it visualises, and really means to treat, as a sort of administrative and clerical hack I would add that it should be obvious from what I have already said that I speak with no personal sense of grievance in this matter, but merely because I see the obvious difficulties and frustrations which might arise had this matter not been very carefully weighed and sifted beforehand, and a firm and binding decision been taken with regard to it

Of the various problems to which the Dean, or other administrative authority, of a Medical School must devote a good deal of his attention, that of the selection of students for entry to the School is one of the most urgent and time-consuming Unfortunately it is also, for reasons which will be discussed below, one of the most unsatisfactory Of the urgency of the task, and also of its magnitude, there can be no doubt, for, whatever be the number of places available in the School, it is certain that the number of applicants will be far in excess of this As to the reasons underlying the phenomenal increase in numbers which has taken place within the last few years there is perhaps little point in arguing, since the situation, whatever the reasons for it may be, is simply one which has got to be faced up to, and dealt with on whatever lines appear to be the most rational to the authorities of the particular School concerned Among factors which have been suggested, however, there may be mentioned (Roberts, 1948) social ambition, the call of idealism, the lowering of financial barriers, and the search for economic security I think there is little doubt that both the first and the last of these are factors of considerable importance at the present time, though whether they will continue to be so under the conditions introduced by the National Health Service Act remains to be seen The actual reality and practical effect of the second factor mentioned—the call of social idealism—is difficult to estimate when one is dealing with the particular age-group in question, that is before personality and interests are fully moulded While I certainly feel that social idealism, or a sense of vocation, are operative factors in a small proportion of cases even at this stage, I see too many applicants who have already made up their minds to be plastic surgeons, psychiatrists, or (rather surprisingly) gynæcologists, to take this very seriously in most cases Taken all in all, it would seem that the most important factor—and indeed that which has in large part allowed the others to become operative—is the lowering of those financial barriers which, even at the time of the Goodenough Report, were reckoned to play an important part in preventing the recruitment of some of the ablest students into the Universities To those unconnected with University administration it may, I think, come as a surprise to learn how profound is the social change which has come about in this regard Even in 1946, when I myself first became immediately concerned with the problem of student selection, it was impressed on one that it was necessary to make careful inquiry into an applicant's financial background—not, of course, that this was to be a major factor, in the average case, in determining his suitability or otherwise for admission, but simply because it had been found as a matter of practical politics that, if suitable enquiries were *not* made in appropriate cases, difficult situations were apt to arise if it became apparent, in the later years of a student's course, that his parents had allowed him to embark on a career which they were in fact not financially able to permit him to complete Nowadays, the scale of State and Local Authority aid available to the majority of students who qualify on academic grounds for admission to a University Medical School is such that I rarely, at the time of selection, give attention to this aspect of things at all , and I can think of few cases in which trouble has resulted Some simple figures may be illuminating in this regard I have divided the students of the Sheffield Medical School, for the Sessions 1938-39 and 1950-51 respectively, into two broad groups—(*a*) " receiving financial assistance " and (*b*) " self-supporting " The line of demarcation is of course not sharp, while the fact that some of the relevant data are of a confidential nature also complicates the investigation Thus, some of the " self-supporting " group may have a relatively small grant, scholarship, or loan, while in the " financially assisted " group no distinction is made between those in whose case the assistance covers fees only and those who receive also maintenance grants. I think, however, there is little doubt that nowadays the payment of fees from public funds is in most cases accompanied also by a maintenance grant. In any case, the broad distinction is between (*a*) those in receipt of substantial financial assistance and (*b*) those predominantly self-supporting. In Session 1938-39, of a total of 172 students, 14 (8.1 per cent.) fell into group (*a*) and 158 (91.9 per cent.) into group (*b*). In respect of Session 1950-51, the position is largely reversed. Of a total of 348 students, 266 (76.4 per cent.) are in group (*a*) and only 82 (23.6 per cent.) in group (*b*). It seems to me that it is probably unnecessary to look very much further for an explanation of the greatly increased numbers of applicants who are now seeking admission to Medical Schools. What these numbers actually are is still a matter of some doubt, since the pressure of competition leads many, probably most, applicants to apply to more than one Medical School. Part of the M.R.C. investigation (Harris, 1948), to which further reference will be made below, is designed to elucidate this particular aspect of the problem—not only because, as Harris points out, an increased number of applications might be due either to more people applying or to the same number of people making more applications (while, equally, a fall in the number of applicants might be concealed by this factor of multiple application), but also because it is of great importance for research purposes to know accurately the total number of applicants to Medical Schools, since the proportion between applicants and places available plays a considerable part in determining the type of selection methods which are likely to be appropriate. Whatever be the upshot of this investigation, the fact remains that all Medical Schools are now confronted with a mass of applications vastly in excess of the number of places available—the ratio of applicants to available places being said to be, in some medical schools, as much as 20 : 1—and the brutal and practical issue must be faced year by year of selecting, from among this mass of applicants, those who are actually to be offered one of the available places. I use the word " offered " advisedly, for one of the complications of the present " multiple application " system is that, when after infinite consideration and labour the offers of places are finally sent out, a variable proportion of refusals is received, from those who have already been accepted elsewhere but who have failed to notify this fact to the numerous other Schools to whom application has also been made. And so the process continues until, perhaps even after the session has actually started, the last place is eventually filled. Some Schools have sought to overcome this difficulty by such means as the charging of " application fees," " reservation fees," etc., or by getting accepted candidates to sign a statement that they have withdrawn all other applications. But it seems clear that none of these methods is a real solution to the problem, and some of us, after trial, have abandoned them, since the extra labour involved did not appear to be justified by the results From time to time the idea has been mooted of some sort of Central Registry to which all applicants would send in their names, at the same time indicating in order their preference for the various individual Schools The central organisation would then arrange, after discussion with the Schools taking part in the scheme, for such interviewing of candidates or other means of selection as might be decided upon, and ultimately furnish each School with a list of those students who had been allotted to it This would seem to provide the only real and lasting relief from the difficulties arising from multiple applications, but it is clear that the very great practical difficulties in creating and operating such an organisation could be overcome only if it had the enthusiastic support of all (or at least most of) the Universities and Medical Schools And this at present seems unlikely to be forthcoming , in the succinct words of a leading article in *The Lancet* (1948), " rightly insisting on freedom in selection, they (*i e* the Universities) often fear that such a device, though voluntary at first, might soon become mandatory, and that central registration would lead to central allocation "

It would appear therefore that there is no hope of early release, so far as most Medical Schools are concerned, from the large and difficult problem which confronts them each year of making what they consider to be an appropriate selection from among the huge number of applicants who desire to enter, and the difficulty of course centres round the problem of what constitutes the basis of " appropriate selection " As has been remarked, " if we have no basis at all, the proper thing would be to throw all the names into a hat and draw out the appropriate number " But the not unreasonable belief persists that there must be some basis better than that of pure chance, and it is the search for this basis which constitutes the core of the problem The initial difficulty is to define exactly what it is that we are looking for in our medical students There is general agreement (Goodenough Report, 1944) that the over-riding factor in selection ought to be " promise of developing into a good doctor " But what in fact do we mean by a " good doctor," what are the qualities which give promise of such development, and how are they to be measured ? A certain level of intelligence is of course important, for it is obvious that, unless a student can first clear the hurdles presented by the medical course and its associated examinations, he can never arrive at the point of beginning the actual practice of his profession, admitted though it be that, in such practice, certain qualities may be much more important than that of pure intelligence—such qualities as, for instance, intellectual honesty, a high moral standard, and willingness to sacrifice personal interest for that of others, together with gifts (Layton, 1948) of a more subtle nature—" the kindly heart, the gentle touch, the control to keep a confidence, the love of children, with the power to make a decision and to accept responsibility " It is clear that a great deal more investigation is called for into what constitutes " a good doctor " Millar (1948) has suggested the undertaking of a " job-analysis " in relation to doctoring He agrees that it would be a very big task, but considers it could usefully be done Others have felt, on the contrary, that, so complex is the business of doctoring, so manifold the characteristics that lead to its being practised well or ill, and indeed so many the different types of career that may be comprised within it, it would defy job-analysis in the ordinary sense, and that empirical studies are more likely to lead to useful results than are methods which at first sight would seem more rational Among the methods which, as has just been said, would appear at first sight to be more rational, are those which are often rather vaguely referred to as " psychological methods of selection " It may, however, be remarked that the most urgent suggestions for the use of such methods come from those whose acquaintance with the use of them is least extensive, or rather, to put it the other way round, that those with the most exact knowledge of, and the greatest experience of, such methods are precisely those who at present advise caution in their use, or at least emphasise that the most urgent requirement at the present time is not the introduction of new methods *as* actual modes of selection, but rather the initiation of really long-term experiments whereby certain data can be collected by appropriate tests, and these data then be checked against the subsequent careers of the persons originally examined

It is satisfactory to know that certain long-term investigations of this type have already been initiated University College, London, was early in the field in this regard, and Smyth's paper (1946), and Bartlett's comments upon it, form a valuable introduction to the problem The Nuffield Foundation, more recently, has launched an experiment designed to last some eight to ten years, whereby an appropriate series of objective tests will be applied to all (not only medical) students seeking entrance to certain selected Universities, further tests of those accepted will be carried out during their University career, follow-up studies will be made of all of these as well as of (so far as possible) those applicants who were not in fact successful in gaining admission, and the question will in due course be investigated of whether or not any correlation exists between the results obtained in the tests applied and " success " at the University and in after-life The tests are designed to cover not only intelligence, but also qualities falling within the domain of character, temperament, and personality The potential value of such an investigation is obvious It is probably generally accepted even at the present time that appropriate intelligence tests can be of value in eliminating those who clearly do not possess the necessary intelligence for a medical career, and therefore that such tests can be of value to selectors in helping to eliminate obviously unsuitable applicants, and therefore in making more time available for the consideration of those not so eliminated But this is probably as far as the matter has gone up to now Intelligence testing is valuable where rapid separation over a wide range of talents is desired, but is of much less help in discriminating between members of a group the majority of whom occupy the upper end of the scale This is, however, a highly technical matter which I myself am not competent to pursue further Besides, as already remarked, a great deal more than intelligence goes to the making of a good doctor, or even of a good student Determination, stability, adjustability to changing situations—all of these may be far more important And the investigation to which I have referred is designed to discover whether objective methods exist, or may be devised, to measure qualities such as these, and to find to what extent these correlate, or otherwise, with success in the chosen profession I am particularly interested in this matter, since the University of Sheffield is one of the centres chosen by the Nuffield investigators for their work I must, however, emphasise that the investigation is purely a test of tests, and in no way a *test of students* The *University authorities, although they on their side furnish (under conditions designed to preserve anonymity* of the students concerned) certain information asked for by the investigators, have no knowledge of what views the latter are forming in relation to any individual, and the investigation plays no part in the University's own selection of students or in the subsequent treatment of those admitted The two procedures are running in parallel, and it will not be for a period of years that it will be known whether the two have been found to correlate, and, if so, how far It is particularly important that this should be appreciated, not only because it is clearly the only reasonable attitude to be taken towards an investigation whose object is to establish the validity, or invalidity, of certain procedures, but because the students themselves must be made to realise this in order to avoid on the one hand their deliberately refusing to take part in the investigation, and on the other hand their indulging in some sort of cramming or coaching beforehand, although I understand the tests are so designed as to minimise this latter effect as much as possible

The *investigation* which I *take* to be *along similar lines*, but restricted to medical students, that is at present being conducted by the Medical Research Council, has been described by Harris (1948) Naturally we should have been greatly interested to co-operate in this, but, our Nuffield programme having been already launched, we felt we had reached the limit to the number of voluntary procedures to which we could properly ask our students to submit—though in this respect it is interesting to note the opinion recorded by Harris that " the willingness of medical students to submit to interviews and tests, administered by some ' snooper ' from outside, is a great tribute to their long-suffering "

The results of the Aberdeen experiment (Millar, 1948) will also be watched with interest, although I understand (personal communication) that its commencement has had for various reasons to be postponed beyond the expected date Here, it is proposed, by means of a comprehensive series of procedures based in general on

War Office Selection Board methods, to gain as much relevant information as possible about each first-year student and to check this against his subsequent performance in the University and perhaps beyond

It seems that, in the long term, much interesting information should become available to us as a result of the investigations described It may be that it will be information which is practical and useful in the sense of indicating that there are objective and scientific methods which could justifiably replace, or at least supplement, the empirical and personal methods on which we are at present forced to rely in the selection of our students , or it may be information which points in precisely the reverse direction , or it may be indecisive But at any rate it will be good to know It is because we are at present working so much in the dark that, in beginning to discuss this question of student-selection, I referred to it as an " unsatisfactory " task It is of course clear that, as regards the really long-term experiment, one of the difficulties will be the selection of the criteria of " success," in respect of which we are going to evaluate the data obtained at an earlier stage At least, however, in the case of a man's undergraduate career, such criteria should be reasonably clear, and, even if all we felt was that we could reasonably prognosticate which applicant would complete his student career satisfactorily and which would not, much would have been achieved If the matter can be carried further, so much the better At present, as Harris (1948) points out, we have advanced little beyond the study made by Sir James Paget in 1869 He found that, of 1000 students traced by him, 23 had achieved distinguished success, 66 considerable success, 507 fair success, 124 very limited success, and 56 had failed entirely , while 41 had died during pupillage, 87 within twelve years of starting practice, and 96 had left the profession The range of talent was exhibited by the fact that the series covered three Professors of Anatomy (Oxford, Cambridge, and Edinburgh), and, at the other end of the scale, two men who had committed suicide under circumstances of great disgrace, together with Palmer, the Rugeley murderer, who was hanged

Pending such accurate information as we hope may, in due course, be forthcoming, it may be of interest if I make, briefly, a few observations on such selection methods as are at present available and commonly made use of —

I find a fairly full type of application form to be desirable—one giving not only basic information, but also some account of the applicant's interests, hobbies and recreations This is not only useful in the preliminary screening of the written applications, but saves time at interview At the latter, however, care must be taken to check the genuineness of the entries , the range of a candidate's real interests often fall far short of what he has professed on paper ! A small photograph attached to the form is most helpful in bringing the individual back to mind when his application is looked at perhaps some time after interview

Naturally a headmaster's report is always given careful attention, though one's attitude towards it must vary somewhat according to whether or not one knows the headmaster in question, or has considerable previous experience of his reports (as, for instance, in the case of local schools) This difficulty, incidentally, might be cited as an argument for having a not too rapidly changing panel of selectors, or for having a permanent chairman of that body (as for example the Dean) who over the years comes to know the characteristics of different headmasters

The question of the applicant's educational background, academic record, and previous examinational achievements, is obviously an important, and at the same time a somewhat controversial one There is of course frequently the practical difficulty that the candidate is sitting some examination (such as, in the past, the Higher School Certificate) in the Session just preceding that in respect of which admission to the University is sought, and the results of this may not be available at the time when the applicant is interviewed In my own Selection Committee the understanding is, in these circumstances, that we rate the candidate on the assumption of an " average " performance in the examination in question, and that I as Dean am given general authority later somewhat to raise, or somewhat to lower, the rating on the strength of an exceptionally good, or an exceptionally poor, examinational performance But of course far more fundamental questions arise in this connection—first, what regard is in general to be paid, in rating a candidate, to apparent examinational ability as opposed to other factors (so far as these can be judged) such as character, temperament, aptitude for a medical career, etc , and second, what kind of educational background is desirable in our future doctors As regards the first of these questions, I suppose that there would be general agreement only on the principle that really poor examinational performance at school should probably be regarded as a contra-indication to admission (It may be objected that *all* candidates who can be considered must at least have satisfied University entrance requirements, and that it is odd to describe such a performance as " really poor " Nevertheless, so great is the competition for places nowadays that nearly all candidates have more than the bare minimum, and many have much more, and I think it would be unfair to the majority to regard only minimal attainments as, for this purpose, other than poor) Much more debatable is the question of whether only average academic attainments combined with apparently the right qualities of character and temperament should be rated as higher or lower than outstanding examinational ability combined with what (in the view of the selectors) are less good qualities in other directions It is of course because of the difficulties in this connection that the whole question of objective procedures in relation to student selection is, as has been indicated above, being so actively explored Few, I suppose, would deny that examinational ability is not the chief factor that goes to the making of a good doctor, and that, given the necessary ability to pass the necessary examinations at the different stages of the medical course, other qualities in the applicant may be far more important But few, on the other hand, would be prepared too lightheartedly to abandon the objective measure of reasonable examinations in favour of subjective procedures in which, unless the selectors be both skilful and conscientious, there is a real danger that mere " likeability " may obscure more significant factors The second question, that of the educational background which we would consider desirable in our medical students, is equally debatable It probably assumes more importance in England, where " First M B exemption " obtained at school bulks so largely in the educational system, than it does in Scotland, where the First M B course and examination are, in normal circumstances, intramural so far as the University is concerned The disquiet which is felt in many quarters in relation to this matter was expressed at a recent meeting of the Royal Society of Medicine (1950) It was there pointed out by the Headmaster of Eton that at some English Medical Schools it is now almost a prerequisite for admission that the student should first have obtained " First M B exemption " , it following as a result that the boy intending to pursue a medical career often had, after the age of fifteen to sixteen, no instruction except in physics, chemistry, and biology This was educationally unsound and indefensible, particularly in view of (as most would suppose) the value of a general cultural background in relation to the practice of medicine These remarks assume a particular pertinence when viewed in conjunction with figures published by Johnson (1949) This observer pointed out that, of students admitted to pre-clinical studies in University College, London, only one-fifth to one-quarter have taken the internal course at the College leading to First M B exemption , the remainder have obtained this exemption externally The U C L selection procedure leading to admission to Second M B courses is very stringent , it is based on the applicant's school record, his performance at a special entrance examination, and interview by a selection board , and the ratio of applications to admissions is about 7 1 Yet, of 41 applicants who in 1948 were offered Second M B places subject to their first obtaining First M B exemption, 18 (*i e* more than one-third) failed in this latter requirement—and one of the 18 had been considered by the selection board to be the most outstanding man interviewed, and had obtained the third highest mark in the special College entrance examination It seems to me that there are good grounds for holding that the tendency which has been so largely followed in England, of supposing the best preparation for a medical course to be early specialisation at school in chemistry, physics, and biology, is a mistaken one On the other hand, I think it would be wrong to underestimate the difficulty, to the student of limited or only average ability, of completing the whole First M B course in the University in one session unless he has *some* previous knowledge of at least chemistry and physics In Sheffield, we are so placed as to make it desirable to allow First M B exemption, and direct entry upon Second Year courses, to a limited number of students , and I do not question this policy in appropriate and selected cases But speaking in general terms, I think it wiser educationally for First Year studies to be carried out within the Universities , for the school curriculum leading up to this to have been as broadly-based as possible, but to have included chemistry and physics up to at least the old School Certificate " credit " standard, with the understanding that this latter proviso can be abrogated in the case of those whose examinational performance in other subjects shows them to be of such exceptional ability as probably to be able to achieve success in the First M B after only one session's work in spite of the handicap imposed by lack of any previous knowledge of the subjects in question I should add that I am impressed by the procedure in vogue at Liverpool whereby it is sought to mitigate the effects of undue specialisation at school by allowing students who have already passed one, or two, of the First M B subjects (and, I think I am right in saying, even some of those students who have complete " First M B exemption ") to enter only the First Year at the University, but there to require them to take only the First M B subject or subjects in which they are lacking, and meantime to allow them to attend, without fee, any other classes in any Faculty which they may choose The eight-term pre-clinical course now under consideration by London University (*Lancet*, 1950) is also a move away from too early specialisation It will (personal communication) abolish " First M B exemption " on school work, the whole eight-term course leading up to Second M B — an integrated one in chemistry, physics, biology, anatomy and physiology—having to be taken intramurally It is true that some previous knowledge of chemistry and physics will be required of the entrants, but only up to Ordinary standard in the new General Certificate of Education, so that there is room for a considerable spread of other subjects at school

This brings me to the last of my sub-heads in relation to the subject of student-selection, namely the interview Most Medical Schools (including my own) regard this as a *sine qua non*, although we are of course prepared to make certain concessions in regard to a small number of applicants from overseas whose suitability appears to be guaranteed by other means It is likely that this (*i e* the importance attached to personal interview) will continue As Harris (1948) aptly remarks, " it is as unlikely that any development in testing practice will supersede it as that laboratory aids to diagnosis will supersede the clinical examination of patients " The role of the interview has already been touched on in discussing the importance to be attached to an applicant's previous examinational achievements, for it is at the interview that the final attempt is made to synthesise all the available information—what the candidate says about himself in his application form, his Headmaster's report, such examination results as are available, and what can be learned at the interview itself about the applicant's character, personality, temperament, sense of vocation, etc —and as a result to give him the rating which will determine his place upon a list and ultimately his chance of acceptance or otherwise It is usual, I think, for such interviews to be conducted by small committees—consisting of say, three—selected for each day from a panel of a larger number It is obviously advisable for the Chairman to be one who attends all, or at least most, of the interviews, in order to ensure as far as possible uniformity of procedure and of standard The chief difficulty, as has already been indicated, is to secure agreement as to the degree of weight to be attached to the various factors considered There can obviously be no finality about this at present That must await the outcome of the various investigations into selection-procedure already described , and of course it is quite likely that there may be no finality even then Still, it is remarkable how much agreement there is, among those who have given considerable thought to this problem, as to how often what appear to be quite reasonable results are arrived at by present methods, possibly because in most Schools there usually seem to be one or more individuals who have what can only be described as a " flair " for this kind of work As Harris (1948) says, " it is unpopular to speak of any form of individual judgment as a reliable instrument, but it seems to me that there can be little doubt that it is sometimes not only reliable but amazingly sensitive " Smyth (1946) has stressed the importance to a School of identifying persons gifted in this way

It would seem that continuance along present lines is all that can be done until much more information is available about the value of other possible methods It is, of course, quite likely that all we can really do at present is to pick out, on the one hand, those applicants whom we are almost certainly right to take, and, on the other hand those whom we are almost certainly right to reject With the number of places available in most Schools, this usually leaves an intermediate zone of varying size in different years So far as the applicants in this zone are concerned, it would probably make little difference if, instead of going through the whole procedure, one simply put the names into a hat and drew out the appropriate number , but of course we cannot know which applicants *are* in fact in this zone unless we have completed the whole procedure in respect of all the applicants whom we want to consider at all

There remains one final point to which, in conclusion, I should like to refer There is an almost universal feeling that, in addition to whatever methods we may adopt in relation to initial selection, there should be a fairly ruthless " weeding-out " of those students who fail to make satisfactory progress in the earlier stages of their University career Certainly it would appear humane that, if a student is going to be in the end invited to discontinue his studies, that invitation should be conveyed to him before he has wasted too much time upon such studies—that is, at the end of the First M B stage, or certainly no later than that of the Second M B Although I of course see the reasonableness of this argument, I sometimes wonder if we are on really sure ground here Does performance in the earlier examinations really correlate well with that in the later? Put more bluntly, is difficulty over chemistry or physics really incompatible with success in clinical work and the academic subjects studied therewith? One may feel specially doubtful about this in view of Johnson's (1949) remarks, already quoted, in relation to the First M B On the other hand, as Johnson has himself agreed, the circumstances of the "external" First M B are rather special, and although data correlating internal First M B results with later achievements are scanty, we have at least the finding of Gibson (1948) in relation to the (internal) First M B at Belfast This observer found that, of those who completed the First M B at the first attempt, most proceeded directly to qualification, whereas most of those who completed it piecemeal failed again later in the course Though Gibson is careful to point out that it has not yet been shown how performance as a student correlates with performance as a doctor, it is comforting to realise that there is at any rate some objective justification for "weeding out" in the early stages

I had originally supposed that, in these random reflections from a Provincial Deanery, I should cover a wider field than I have in fact done, for it must not be thought that my energies are entirely devoted to wondering, in the first place, whether I ought to exist at all, and in the second place whether we are going about our selection of students in the best way There are of course many other problems at which it might have been profitable to glance, but I fear that time will not permit of that being done to-night I confess that I feel somewhat humbled in looking at the list of the titles of the lectures that have already been given in this series There seem to be so many people who know so much about such intricate subjects that it gives one the feeling of being—how shall I put it?—rather a dunce among the learned I can only hope that something which is, I think, a little off the usual lines, and presented by a worker in rather a different field, may perhaps have been not without interest to some of my hearers

REFERENCES

BARTLETT, F C (1946), *Brit Med Journ*, 2, 665

GIBSON, Q H (1948), *Lancet*, 2, 323

HARRIS, A D (1948), *Lancet*, 2, 317

Report of the Inter-departmental Committee on Medical Schools (1944) London H M S O

JOHNSON, M L (1949), *Lancet*, 2, 529

Lancet (1948), 2, 337

Lancet (1950), 2, 529

LAYTON, T B (1948), *Lancet*, 2, 432

MILLAR, W M (1948), *Lancet*, 2, 327

ROBERTS, FF (1948), *Lancet*, 2, 431

Royal Society of Medicine, Report of Meeting (24th October 1950), *Lancet*, 2, 501 *Brit Med Journ*, 2, 1052

SMYTH, D H (1946), *Brit Med Journ*, 2, 357

THIRTY YEARS' EXPERIENCE OF THE MEGALOBLASTIC ANÆMIAS

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DURING the past eighteen months, many discussions have taken place at medical societies and many reports have appeared in the medical press about the roles of vitamin B_{12}, folic acid and folinic acid in the maintenance of normal hæmatopoiesis and the mechanisms and pathways by which they subserve this purpose through their influence on the metabolism of nucleic acid I believe it is true to state that any opinions expressed on these matters at the present time are largely hypothetical, as information based on acceptable data is still insufficient to warrant the formulation of any definite conclusions Accordingly, I do not propose to deal with this aspect of the pathogenesis of the megaloblastic anæmias but shall utilise the short time allotted to me for discussing a few personal impressions and experiences of a group of anæmias with which I have been interested and intrigued for a period of more than thirty years *

My experience of hæmatology falls naturally into three periods The first covers my work in Edinburgh during the years 1919-29, the second my occupancy of the Regius Chair of Medicine in Aberdeen from 1930-38, and the third occupies my term of office as Professor of Medicine in the University of Edinburgh from the time of my return to that city in October 1938 until the present time

PERIOD 1, EDINBURGH, 1919-29

It was my good fortune as a young doctor to be successively Assistant, Clinical Tutor and Assistant Physician, first with Professor Gulland and later with Dr Goodall, who during that period were the leading hæmatologists in Great Britain It is, therefore, not surprising that I became interested in this speciality at an early age The particular aspect of this period which I should like to discuss briefly is the difference which I have noted in the clinical picture of the cases of pernicious anæmia seen by me in the wards of the Royal Infirmary in Edinburgh prior to 1927 as compared with the patients in my wards in Edinburgh in 1951 Between 1919 and 1926, when the discovery of liver therapy was announced, I had the opportunity of studying the clinical features and watching the course of many cases of pernicious anæmia in Professor Gulland's wards until they reached their fatal termination The description of the disease in many textbooks of medicine in use to-day is still largely based on the clinical picture seen before the introduction of liver therapy The failure to appreciate the fact that many clinical features, formerly held to be of great diagnostic value are rarely encountered to-day, is a potent cause of delay in diagnosis and the institution of proper treatment Last year I asked Dr Newall, one of my Assistants, to examine the case records and classify the clinical features of a consecutive series of 135 cases of pernicious anæmia seen at my Blood Clinic during the period 1944-48, and compare them with any reports that he could find in the literature of the clinical features as they existed prior to 1925. The following information obtained from Dr Newall's analysis and from my own experience may therefore be of some interest

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* This paper is based on a lecture on the megaloblastic anæmics delivered to the Royal Society of Medicine

Age of Onset —More patients are apparently developing the disease in older age groups nowadays than they did fifty years ago Thus the onset of the disease occurred between the age of sixty and eighty years in no less than 42 per cent of our cases seen during the period 1944-48, as compared with 18 per cent of the 110 cases reported by Cabot in 1900

Another point of interest investigated by Dr Newall was the *duration of the disease before the patients were referred for a hæmatological opinion* It was found that 37 per cent of our recent patients had had symptoms for three months or less, 70 per cent for six months or less and 80 per cent for twelve months or less before being referred to our Blood Clinic In contrast, Panton (1923) stated that the average duration of symptoms before obtaining a hæmatological opinion was nteen months It is obvious that early diagnosis will be an import- factor in influencing the accepted clinical picture of pernicious a

Glossitis —Prior to 1927 the majority of patients dying of pernicious anæmia in Professor Gulland's wards had acute glossitis as indicated by the fiery red colour of the tongue and the presence of ulceration These appearances were seen in about 5 per cent of our recent series of 135 cases On the other hand, a smooth atrophic tongue was present in approximately 80 per cent of these cases It should be pointed out that the features of atrophic glossitis in pernicious anæmia are indistinguishable from the changes in the tongue which are frequently seen in women suffering from chronic nutritional iron-deficiency anæmia

Diarrhœa for which no obvious cause can be found was a very characteristic feature of pernicious anæmia twenty-five years ago In our recent series, diarrhœa occurred in only about 10 per cent of cases in contrast to the incidence of 30 and 40 per cent mentioned in the reports of Panton in 1923 and Cabot in 1900 respectively Our case notes suggest that constipation occurred twice as frequently as diarrhœa, while minor alimentary upsets such as mild anorexia, dyspepsia or flatulence were commonly noted

Clinical Jaundice, which was present in nearly every patient dying of pernicious anæmia twenty-five years ago and on which so much stress was laid as a diagnostic feature, is very much less frequently encountered to-day Jaundice seldom becomes obvious until the red-cell count has fallen below 1½ millions, hence its presence is an indication that diagnosis has been regrettably delayed either because the practitioner has been incorrectly educated in regard to its clinical significance or else because insufficient hæmatological facilities are available to him in the region in which he works

Ataxia —In contrast to twenty-five years ago, when ataxia was a common presenting complaint, it was rarely noted in the series seen in Edinburgh during 1944-48 Only one patient out of 135 stated that the reason why he initially consulted his doctor was because of unsteadiness on walking Signs suggestive of involvement of the posterior columns of the spinal cord were found in approximately 10 per cent of cases, although a complaint of subjective sensations such as numbness and tingling in the limbs was made by one out of every three patients

Splenomegaly —In my experience of the disease prior to 1927, a palpably enlarged spleen was present in at least 30 per cent of cases, while in our series of cases recently investigated in Edinburgh the spleen could be felt in less than 10 per cent of cases The enlargement, when present, was only moderate in degree and could usually only be detected on deep respiration

Sufficient has been said to make it clear that the clinical picture of the disease, so frequently seen prior to the discovery of liver extract, as indicated by clinical jaundice, acute glossitis, diarrhœa, ataxia and splenomegaly, can no longer be accepted as being satisfactory if early diagnosis is to be achieved and adequate treatment instituted before the development of serious complications (see Table I) The main presenting features seen in cases of pernicious anæmia at the present time are weakness, dyspnœa on effort, vague dyspepsia, pallor of the skin and especially of the mucous membranes It should be stressed in textbooks of medicine that the diagnosis of pernicious anæmia cannot be made solely by physical examination or on the presenting features of the disease, since these are not pathononomic of any particular type of anæmia A competent hæmatological examination is the only method which will enable the correct diagnosis to be made

The second impression of this period which will ever remain vividly in my memory is the thrill which I got from treating my first case of pernicious anæmia with liver in 1927 Only those who have watched the inevitable progress of this fearful disease to its fatal termination prior to the introduction of liver therapy, can appreciate the amazement and delight with which we noted the extraordinary change in the patient's sense of well being and the return of a pink colour to the pallid lemon-yellow face which occurred within a few days of the commencement of treatment Twenty-five years ago there were no hæmatological technicians in the Royal Infirmary, Edinburgh, and accordingly at that time, and for many years after, I had to undertake all necessary blood investigations myself This at least gave me the great personal satisfaction of observing for the first time the dramatic rise in the reticulocyte count which commenced about the fifth day of oral liver therapy Although the reticulocyte had been described for many years before the discovery of liver therapy, the reticulocyte count only received general acceptance as a valuable test for the assessment of therapeutic agents in hæmatology subsequent to the appearance in 1926 of Minot and Murphy's report on the treatment of pernicious anæmia with liver

TABLE I

The Clinical Features of Pernicious Anæmia Prior to 1927 *and After* 1944

	Edinburgh 135 cases (1944-48)	Cabot 110 cases (1900)
Percentage of patients aged over 60 years at onset	42%	18%
Duration of symptoms before the patient was submitted for a hæmatological opinion	Under 3 months—37% Under 6 months—70% Under 12 months—80%	Panton (1923) average duration 17 months
CLINICAL FEATURES		
Acute glossitis (red ulcerated tongue)	5%	Edinburgh (prior to 1927) very common
Chronic atrophic glossitis (pale smooth tongue)	80%	=
Diarrhœa	Less than 10%	Edinburgh (prior to 1927) very common Panton (1923)—30% Cabot (1900)—40%
Clinical jaundice	Uncommon	Edinburgh (prior to 1927) very common
Involvement of C N S	Less than 10%	Edinburgh (prior to 1927) very common
Splenomegaly	Less than 10%	Edinburgh (prior to 1927) 33%
Weakness and tiredness	100%	=
Dyspnœa on effort	80%	=
Vague dyspepsia	50%	=
Pallor of mucous membranes	100%	=

PERIOD 2, ABERDEEN, 1930-38

On arrival in Aberdeen in 1930, I found that the Department of Medicine consisted solely of a lecture room and a retiring room and that the staff allocated to the Professor consisted of one part-time Assistant My request to the University authorities for laboratory accommodation was granted and temporary buildings were rapidly erected, while preparations were made for the erection of a new hospital and medical school A great deal of my time was devoted to these developments, but unfortunately I had the pleasure of working for less than two years in these splendid new buildings before I was recalled to Edinburgh in 1938 During my period of office in Aberdeen I was very fortunate in my selection of staff for the Department of Medicine The first Assistant whom I chose was Dr McMichael, now Professor of Medicine in the Post-graduate Hospital, Hammersmith, London, the second was Dr Hill, now Professor of Medicine in Dundee, and my third was Dr Fullerton, who is the present occupant of the Chair of Medicine in Aberdeen

Of the many hæmatological experiences in Aberdeen, three stand out prominently in my memory despite the lapse of time The first was an attempt to produce an extract from fish livers on a large scale I had high hopes not only for the therapeutic value of such an extract in pernicious anæmia, but also for its commercial value as a new enterprise which might help the fishing industry which was in a state of grave depression and unemployment at that time The first step was to obtain the help of an industrial chemist to solve the problem of how to extract the oil from fish liver without damaging the oil or the residue from which would be secured the anti-pernicious anæmia principle The second step was to establish a satisfactory method of extracting the anti-anæmic principle from the fish residues in a potent and palatable form The third step was to prove the potency of the liver extract by clinical trials on patients, and the last step, if the first three were successful, was to persuade an industrialist to set up a large-scale manufacturing plant Complete success attended the first three steps of this enterprise, a palatable product was produced from fish livers which induced excellent clinical and hæmatological results in patients with pernicious anæmia in a dose as low as a teaspoonful thrice daily (Davidson, 1932) It is therefore sad to relate that all these efforts came to nothing and the enterprise had to be abandoned because it became apparent just when commercial production of fish liver extract was about to start that oral liver therapy would be permanently supplanted by parenteral liver therapy which had been shown to be so much more effective

The second experience to which I should like to refer is connected with the interesting problem of the megaloblastic anæmias refractory to the parenteral injection of potent refined liver extracts My investigations into this problem, which have been proceeding for nearly twenty years, originated in Aberdeen as a result of certain observations which I made on a case of megaloblastic anæmia associated with the tropical sprue syndrome The patient had a fatty diarrhœa and had lost six stones of weight within the twelve months prior to admission to my unit The blood count was under one million red cells and the blood picture was typical of pernicious anæmia The patient failed to respond to the injection of ample amounts of Campolon and Anahæmin and would undoubtedly have died if I had not put him on to a high protein diet containing half a pound of liver daily by mouth

A remarkable hæmatological and clinical remission resulted, including the return of free hydrochloric acid to the gastric juice On the basis of these observations, I suggested nearly twenty years ago that the chemical fractionisation of liver extracts for parenteral use removed some essential factor which was necessary for the restoration of normal blood formation in certain types of megaloblastic anæmia Many years were to elapse before the discovery of folic acid was made This claim has been confirmed in many parts of the world and has been shown to be equally applicable to vitamin B_{12} which is also an ineffective therapeutic agent in certain types of megaloblastic anæmia A series of reports have been published from my department during the past twenty years dealing with various aspects of the refractory megaloblastic anæmias associated with pregnancy, malnutrition, malabsorption and from no known cause

The third and last impression I have of my work in Aberdeen is connected with a group of anæmias due to iron deficiency Unemployment was rife in the city and large numbers of women were referred to our Blood Clinics with hypochromic anæmia of great severity. It soon became apparent to me that however intriguing and exciting were the megaloblastic anæmias, their rarity compared to the iron deficiency anæmias made them of little economical or sociological importance in this community It was the realisation of this point that induced Fullerton and myself to undertake a large-scale assessment of the hæmoglobin levels of an unselected section of the community comprising individuals of both sexes and all ages from infancy to old age Nearly 3000 unselected individuals had their hæmoglobin levels estimated and the results were published with an accompanying graph (Davidson, Fullerton and Campbell, 1935) It is my belief that this paper and its graph fulfilled a useful purpose in bringing the attention of the medical profession not only in Great Britain but in other parts of the world to the great frequency of iron deficiency anæmia, its sociological and economic implications and to the vulnerability of certain groups to this form of anæmia, namely infants and women of the child-bearing age

PERIOD 3, EDINBURGH, 1939-51

One of the most interesting medical changes which has occurred in Edinburgh during the past twenty-five years is the great expansion and improvement of the facilities for the investigation and treatment of diseases of the blood available to the doctors and their patients in the South-East region of Scotland Up to the time of the retiral of Professor Gulland in 1928, his staff consisted of one part-time assistant paid by the University, and one part-time Clinical Tutor paid by the Royal Infirmary There was no laboratory accommodation available to him and his staff either in the Department of Medicine or in the Royal Infirmary When his successor, Professor W T Ritchie, retired in

1938 the Department of Medicine in the University contained five rooms, fitted up as laboratories and offices, and a large demonstration room for teaching purposes, while the staff consisted of one full-time Lecturer and two Assistants At the present time the accommodation of the University Department of Medicine is more than double that available to my predecessor, while my staff includes 7 full-time Lecturers, 4 part-time Lecturers, 4 full-time Assistants in addition to a large number of Registrars and Senior House Officers working in the Professorial Medical Units located in various hospitals in Edinburgh The need for a great increase in staff was accepted by the University Court when it approved of my policy of developing special units for teaching and research in hæmatology, rheumatology, gastro-enterology, cardiology, neurology, nutrition and diseases of the respiratory tract In the division of hæmatology, I have a medical staff of one full-time and two part-time Lecturers, two Assistants, and one hæmatological Registrar, while the non-medical staff consists of four technicians trained in hæmatological methods In addition to accommodation located in the University and in the Clinical Research Laboratory in the Royal Infirmary, the Board of Management of the hospital has provided me with consulting rooms, waiting rooms, offices for secretaries and for filing records, and hæmatological laboratories for servicing the special clinics for the investigation and treatment of diseases of the blood It would indeed be extraordinary, therefore if the services available in Edinburgh at the present time were not incomparably superior both in quantity and quality to those in operation twenty-five years ago, when a part-time Professor of Medicine, who was fully occupied by a vast consulting practice, was provided with one part-time Assistant and no laboratory accommodation in hospital

Many thousands of patients suffering from all kinds of blood disorders have been referred to my unit for a hæmatological opinion during the past eleven years A survey of this mass of clinical material makes it clear that the megaloblastic anæmias comprise a relatively rare group of blood diseases During this period (1940-51) we have seen 713 cases of macrocytic anæmia as judged by the colour index and mean cell volume being above the upper limits of normal Table II shows that 577 of these cases were proved to be associated with a megaloblastic marrow While it is obvious that all macrocytic anæmias are not necessarily megaloblastic, it is true to say that in Scotland the chance appears to be about 5 1 that macrocytosis of the circulating erythrocytes will be associated with megaloblastosis of the bone marrow Table I also clearly shows that Addisonian pernicious anæmia is by far the commonest type of megaloblastic anæmia in Scotland

The Megaloblastic Anæmia of Pregnancy —Sufficient time remains for me to deal only with one group of the megaloblastic anæmias, namely that associated with pregnancy and the puerperium During the past eleven years, we have studied 42 cases belonging to this group The rarity of this form of anæmia is emphasised by the fact that we encounter in Edinburgh only one case of the megaloblastic anæmia of pregnancy for every 18 cases of Addisonian pernicious anæmia, which in itself is an uncommon disease Dr Clark, one of my Lecturers in hæmatology, has recently made a careful study of 18 cases of megaloblastic anæmia, investigated in my unit during the past seven years, with the object of seeing whether they differ in any material respect from some 16 cases which we reported in the *British Medical Journal* ten years ago (Davidson, Davis and Innes, 1942) The result of this investigation will be appearing in the near future in the *Edinburgh Medical Journal* The principal features previously noted by us have been again confirmed, namely —

TABLE II

Macrocytic Anæmias 1940-51

Diagnosis —	
Addisonian pernicious anæmia	489
Mal-absorption syndrome	61
Megaloblastic anæmia of pregnancy	42
Idiopathic refractory megaloblastic anæmia	14
Hypoplastic anæmia and aplastic anæmia	25
Hæmolytic anæmia	21
Miscellaneous, including diseases of the liver	61
Total number of cases of macrocytic anæmia	713

Of these, the following have been found to have a megaloblastic marrow —

1 Addisonian pernicious anæmia	489
2 Megaloblastic anæmia of pregnancy	42
3 Megaloblastic anæmia of the mal-absorption syndrome (*a*) Tropical sprue (*b*) Idiopathic steatorrhœa (*c*) Post-gastrectomy (one case)	30
4 Idiopathic refractory megaloblastic anæmia (refractory to parenteral liver therapy for no ascertainable cause)	14
5 Megaloblastic anæmia of liver disease	2
Total number of cases of megaloblastic anæmia	577
Total number of cases of macrocytic anæmia with normoblastic marrow	136

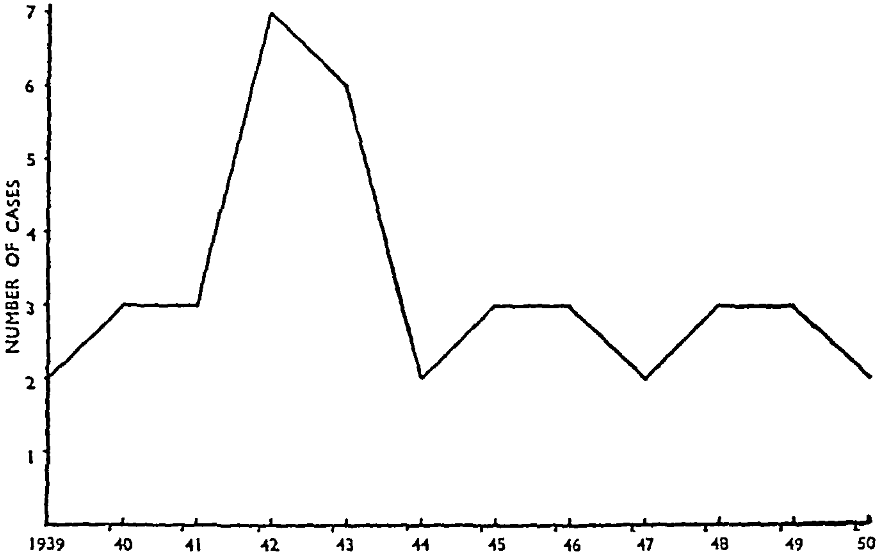
(1) the need for examination of the bone marrow for diagnostic purposes, because of the frequency with which the colour index and mean cell volume may be within or even below the values accepted as normal,

(2) the frequency with which free hydrochloric acid is found in the gastric juice, and

(3) the refractoriness of this group of megaloblastic anæmias to the parenteral injection of liver extract or vitamin B_{12}, and their immediate response to the oral ingestion of proteolysed liver or folic acid

Dr Clark has also estimated the ratio of cases of megaloblastic anæmia of pregnancy developing in women admitted to the Simpson Maternity Hospital, Edinburgh, over a period of seven years in relation to the number of deliveries over the same period. He concludes that the disease occurs in about one in every two thousand pregnant women admitted to this Maternity Hospital. He also draws attention to the rarity of the disease as indicated by the fact that out of the many hundreds of cases of anæmia investigated in the Blood Clinic in Edinburgh every year, only two or three belong to this group. I have constructed a graph (see Graph 1), to indicate not only the rarity

Annual Incidence of Megaloblastic Anæmias of Pregnancy and the Puerperium in Edinburgh 1939-50



GRAPH 1

of the disease, as judged by its average annual incidence during the past seven years, but also the remarkable fact that during the period 1941-43 the incidence of the disease in Edinburgh appears to be two or three times as great as in recent years. Is this finding to be dismissed as being purely fortuitous or is to be attributed to the fact that during these years Britain's war-time diet was at its lowest nutritional level in many respects and especially in animal protein? From 1943 onwards, when the submarine danger was being gradually controlled, not only were Britain's nutritional requirements more adequately satisfied by imports from overseas but the general standard of nutrition of the poorer sections of the nation, who prior to the war existed in the shadow of unemployment or partial employment, markedly improved consequent on full employment, higher wages and a more equal distribution of nutrients through the channels of rationing, school meals and special social services.

mild degree of hæmolytic anæmia Subsequent to delivery she continued to suffer from acholuric jaudice, and accordingly some months later she was treated with ACTH without any effect on the hæmolytic process, and later by splenectomy with entirely successful results It is reasonable to suppose that the additional strain of pregnancy lead to the development of a megaloblastic anæmia by increasing the needs for hæmopoietic factors in a patient whose requirements were already greater than normal because of pre-existing hæmolytic anæmia

In conclusion, I would like to express my gratitude to Providence for the fortunate chance which lead me as a young man into the fields of hæmatology, as in my opinion no branch of medicine during the past thirty years has offered greater or more exciting opportunities to the clinician and the research worker

REFERENCES

CABOT, R C (1900), *Amer Journ Med Sci*, 120, 139
PANTON, P N *et al* (1923), *Lancet*, 1, 274
DAVIDSON, L S P (1932), *Brit Med Journ*, 2, 347
DAVIDSON, L S P FULLERTON, H W, and CAMPBELL, R M (1935), *Brit Med Journ*, 2, 195
DAVIDSON, L S P, DAVIS, L J, and INNES, J (1942), *Brit Med Journ*, 2, 31
DAVIDSON, L S P, GIRDWOOD, R H (1951), *Lancet*, 2, 1193
OWREN, P A (1948), *Blood*, 3, 231

DERMATOMYOSITIS A CASE REPORT

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DERMATOSITIS is a non-suppurative inflammation of skeletal muscle, skin, sometimes the myocardium, and occasionally accompanied by lesions of the alimentary tract Diagnosis in life is often difficult, for which reason, together with its comparative rarity, the case about to be described is thought worthy of publication

The ætiology is still obscure and many authors regard it as directly or indirectly of infective origin O'Leary, Warsam, and Morris believe that antecedent acute infections, focal sepsis, pulmonary disease or parturition play a prominent part For 5 out of 40 cases they claimed to isolate streptococci, which, when injected into animals, produced hæmorrhagic lesions of skin and muscle Lamb described a case in which complement fixation tests against streptococci were positive, and the patient's blood agglutinated autogenous streptococci from the nasopharynx Holmes recorded the recovery of streptoviridans from the muscle of a histologically proven case, although he was unable to culture an organism from the blood

Nevertheless, in spite of these facts the role of bacteria in this disease appears as problematical as in rheumatoid arthritis and the so-called " collagen diseases "

The age period at which the disease occurs varies from childhood to old age with a maximum incidence at the fifth decade, but the incidence is roughly equal in the two sexes

Clinically, the diagnosis may be extremely difficult because of the various modes of onset In some the dermal lesions appear first, in others the muscular, or both components may appear together Finally, vasomotor symptoms of the Raynaud type, or simulating vascular thromboses may open the story In Lewis' case thromboses were ultimately demonstrated

The dermal manifestation may start as a diffuse erythema similar in appearance and distribution to lupus erythematosus, or as in the author's case, it may resemble pityriasis rubra In the case described by Holmes a musculo-erythematous rash with petechial hæmorrhages developed over the limbs , Goldman's patient suffered a vesiculated keratotic eruption of the extremities Œdema usually accompanies the florid exanthemata, and with the passage of time the lesion becomes widespread and scleradermatous

The muscular symptoms may effect any part, but predominently the shoulder girdle, arms and neck Eventually the entire voluntary muscular system may appear involved—pain, progressive wasting, and profound weakness The downhill course is generally relentless until death due to respiratory or pharyngeal myopathy terminates the issue The rate of progress is very variable, however, the patient may be dead in a few months, or, waxing and waning, linger on for five or six years

The morbid anatomical and histological features are well exemplified by the following case in which, however, the dermal lesions preceded the muscular, and never reached the sclerodermal stage

CLINICAL HISTORY

Mr A K, aged 36 at time of death

In November 1948 a skin eruption commenced over the hands and feet In February 1949 Dr A S Hall saw the patient for the first time, and noted a diffuse erythema of the hands and feet, wrists, forearms, shins, knees, groins and genitalia, with considerable thickening and scaling Marked fissuring at the joint folds limited movements

The scalp was also covered with scales and thickened, although there was no loss of hair The angles of the mouth were fissured and the buccal mucosa reddened, thickened and denuded

Generalised lymphadenopathy and œdema of the ankles was present, but without visceral enlargment No abnormality of muscle power, the blood picture, urine, or radiological appearance of the chest *A diagnosis of Pityriasis Rubra was made*

Shortly after this time "pins and needles" developed in the forearms, together with numbness in the middle fingers of each hand

By June 1949 symptomatic treatment had greatly improved the skin lesions although erythema remained, increasing muscular weakness with wasting (upper limbs), kyphosis, dysphagia and dyspnœa now became evident, nd a diagnosis of dermatomyositis was now considered by Dr Hall and Dr M Robertson A month later, due to weakness of the neck muscles, the atient was unable to hold his head up, and complained of a sense of dull pressure about the neck and left shoulder The muscular symptoms tended to be relieved by rest He had lost about two stone since leaving the army, but his appetite and digestion were normal Nothing relevant in his past history

On 3 8 49 it was noticed that the hands, feet, and nails showed marked parakeratosis, but diffuse erythema with desquamation was present on the distal halves of all four limbs

By September 1949 his condition had deteriorated and on examination showed —

C N S—Cranial nerves —Normal apart from doubtful weakness of the right facial muscles, wasting of the trapezius muscles and tongue

Upper and lower limbs —Marked muscular wasting and weakness, maximal proximally, and symmetrical, tendon reflexes normal apart from absence of knee jerks

Abdominal and plantar reflexes —Normal

No abnormalities of the sensory system, no tremors or muscular fibrillation

Marked wasting of neck and shoulder muscles, especially trapezei, scapular and posterior cervical

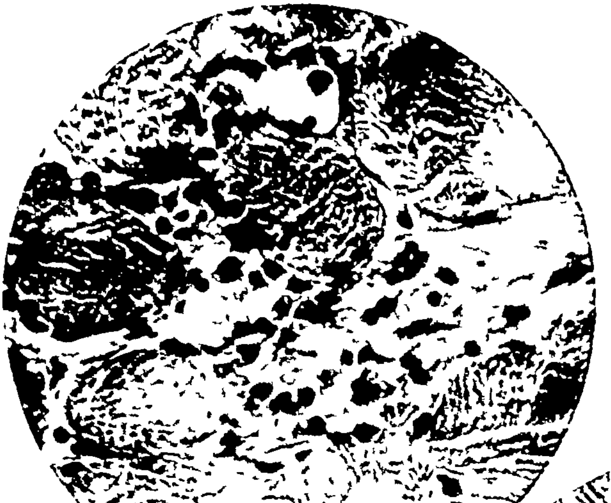

Fig 1 —Biopsy one month before death Noted isolated interstitial lesion High power view

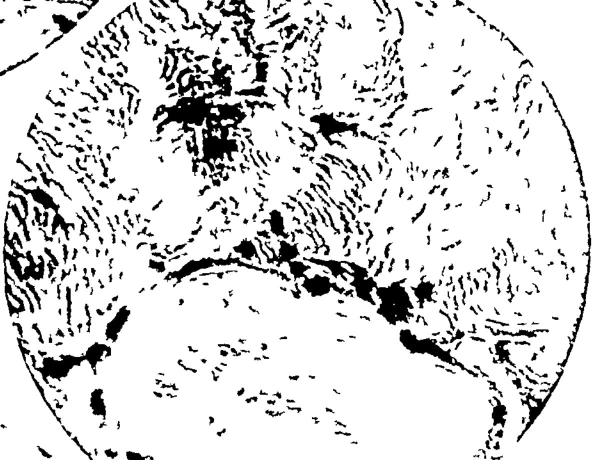

Fig 2 —Biopsy one month before death Note solitary hyaline muscle fibre in centre High power view

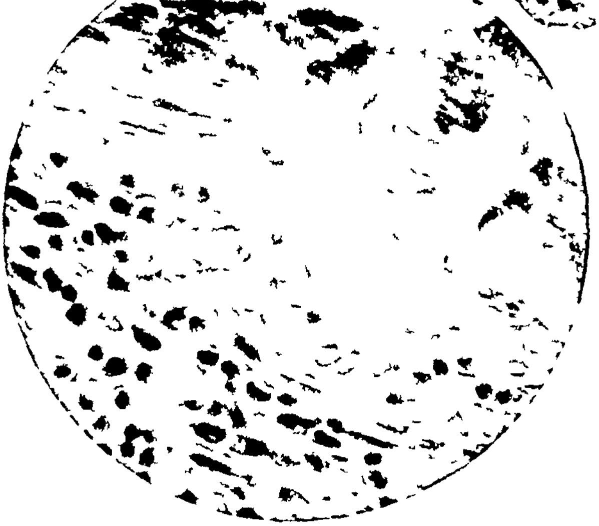

Fig 3 —Section taken at autopsy Interstitial infiltration by round cells High power view

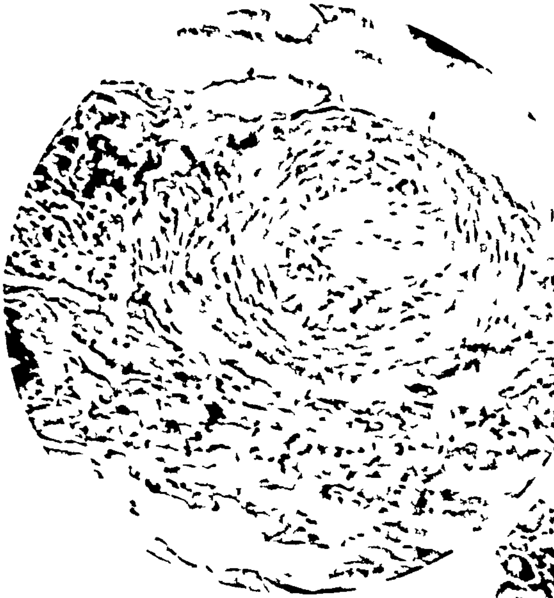

FIG 4 —Section taken at autopsy Vascular lesion showing marked endarteritis Low power view

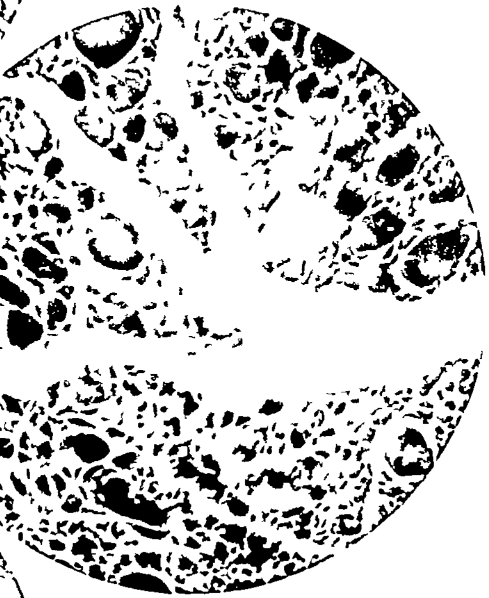

FIG 5 —Section taken at autopsy Skeletal muscle showing marked discrepancy in size of muscle fibres Low power view

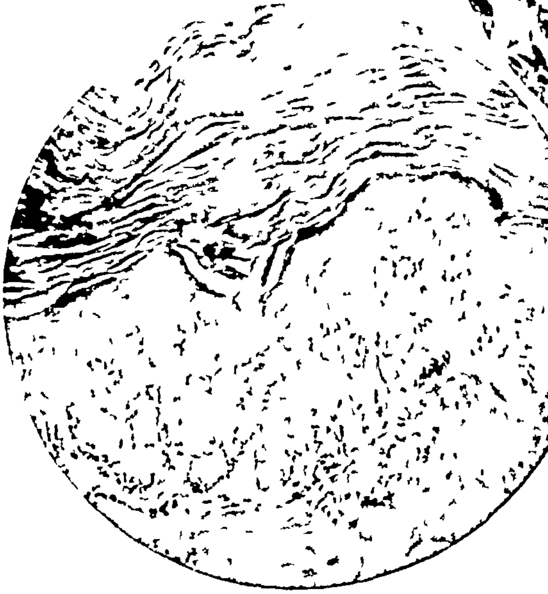

FIG 6 —Section taken at autopsy Note hyperkeratosis and diffuse round cell infiltration of corium Low power view.

Cardiovascular and respiratory systems, and abdomen —Normal
Temperature —Normal

Investigations

Blood Counts —Hb varied between 78 and 90 per cent White cell counts —

17 2 49 W b c 10,400 per c mm (polymorphs 76 per cent , lymphocytes 16 per cent , monocytes 4 per cent , eosinophils 2 per cent)
27 5 49 W b c 8000 per c mm (polymorphs 75 per cent , lymphocytes 19 per cent , monocytes 3 per cent , eosinophils 3 per cent)
29 7 49 W b c 7600 per c mm (polymorphs 66 per cent , lymphocytes 22 per cent , monocytes 5 per cent , eosinophils 6 per cent , basophil 1 per cent)

C S F—29 7 49 Chlorides 740 mgms per cent Protein 25 mgms per cent Sugar 65 mgms per cent No cells seen W R negative Lange normal

Surgical Biopsy (29 7 49) —Section of left pectoralis major —" In the main the muscle fibres appear normal but interstitial collections of round cells (mostly lymphocytes), together with scanty and pyknotic polymorphs form fairly numerous foci Where these occur the muscle fibres appear a little more hyaline than elsewhere Although the round cell foci are usually associated with dilated capillaries there is nothing resembling actual arteritis In places the foci appear associated with nerve tissue although not all nerve elements are affected

The possibilities in my opinion are —

1 Polyneuritis
2 Myasthenia gravis
2 Polyarteritis (A typical lesion not having occurred in this section)

Muscle Intensity Duration Curves (3 8 49) —

Normal graphs, *i e* normal conductivity in nerves and normal excitability of muscles

X-rays —Chest, skull, cervical and dorsal spine —normal

On 31st August the patient was seen by Dr J St C Elkington at St Thomas's Hospital , he suggested a possible diagnosis of dermatomyositis in which the original skin lesion was settling with very little chronic sclerodermatous change The patient was returned to Winchester, where early in September he was temporarily discharged to his home to settle personal affairs While there he died suddenly

AUTOPSY REPORT (29 9 49)

Short stature , narrow build wasting of skeletal muscles generally, but maximally in shoulder girdles, upper limbs, and thoracic muscles Marked thickening of all digital nails

Marked hyperkeratinisation of soles of feet and both hypothenar eminences No identifiable cutaneous eruption

Dissection of skeletal muscles —Marked pallor of those about the thorax and upper limbs, except where post-mortem lividity is evident over the dorsum

Serosæ

Peritoneum and pericardium —Normal Pleuræ, normal apart from a few adhesions on left side along anterior border of upper lobe

Tongue —Lymphoid tissue at its root is unduly prominent

Pharynx and Larynx —Normal

Trachea and Main Bronchi —Contain abundant muco-pus, bronchi appear congested

Thyroid —Normal

Mediastinal Lymph Nodes —Paratrachial, tracheo-bronchial and broncho-pulmonary on both sides appear a little enlarged, congested and œdematous

Lungs —No acute pleurisy Both organs appear congested, œdematous, and show extensive broncho-pneumonia mainly in lower lobes

Heart —300 gm in weight

Pericardium —Normal The myocardium, valve cusps, endocardium and coronary arteries are normal

Aorta and Pulmonary Artery —Normal including valve cusps

Cœliac Axis, *Splenic Artery*, *etc* —Normal

Adrenals, pancreas, œsophagus, stomach, duodenum, small and large *Intestine* —Normal

Spleen —260 gm Nearly twice normal size, normal shape Section, malphigian bodies appear extremely numerous and a little enlarged, they almost resemble those in " sago " spleen

Liver —2371 gm Enlarged Normal shape Section, general appearance of cloudy swelling

Urinary Tract —Normal apart from vascular congestion of the kidneys

Prostrate and Rectum —Normal

Superficial and Abdominal Lymph Nodes —Normal

Brain —Externally and on section it appears normal

Histology

Skeletal Muscles —Sections taken from the pectoral, dorsal, trapezius and paoas muscles are extremely striking The changes observed are advanced but may be divided into those of (*a*) muscle fibres, (*b*) interstitial tissue, (*c*) arteries

The majority of muscle fibres are affected to a greater or lesser degree, initially they show an apparent increase in sarco-lemmal nuclei, together with separation of the myofibrils Here and there a muscle loses its transverse striations and becomes completely hyaline, while in transverse section some exhibit a central vacuole In more severely affected parts the muscle fibres undergo longitudinal splitting, become zig-zag in shape, and finally are broken into small fragments which tend to take on a bluish colour with hæmatoxylyn-eosin, they are obviously being phagocytosed by mobile cells of the interstitium In some parts of a particular section myolysis is less evident, but the mucle fibres become completely hyaline and converted to collagen Muscle fibres of widely varying sizes may be seen in the same low power field

The interstitial changes are very variable, in places there is intense cellular infiltration by mobile elements, predominently mononuclear—lymphocytes, plasma cells, elongated or polygonal sarcoblasts In other parts the interstitium is only moderately cellular but appears swollen and œdematous, so that muscle fibres are widely spaced apart Finally, in the most advanced lesions fibrosis obliterates both cellular interstitial tissue and muscle fibres

The vascular lesions are those of endarteritis medial and intimal thickening (the latter in part may be due to œdema) The vessels involved are the small arteries and arterioles, but the interstitial inflammation is not obviously perivascular, and there is minimal evidence of invasion of the vessels by mobile cells, or their implication by necrosis of the polyarteritis nodosa type

Skin—Sections from the plantar surface of the foot and palm of the hand show marked hyperkeratosis, diffuse low grade round cell infiltration in the subepithelial papilla, together with a few perivascular round cell infiltrations in the deeper corium, medial and intimal thickening is seen in some small arteries Here and there fragments of underlying striated muscle show marked hyaline change, but without pronounced cellular reaction around them

The skin over the scapula exhibited more definite abnormality—the epithelium is thin but the underlying corium is dense and contains fairly numerous " lymphorrages," *i e*, perivascular round cell collections Arterial changes as above are also present

Tongue—Fairly severe myositis together with round cell infiltration of the corium The squamous epithelium shows excessive " scaling " and appears acanthotic

Larynx—Shows a diffuse round cell infiltration beneath the epithelium, and a low grade myositis

Heart—Sections from right and left ventricles appear normal

Lung—Acute broncho pneumonia

Spleen—Shows changes characteristic of septic spleen

Liver, Kidney, Adrenal and Brain—Congestion and post-mortem autolysis

Axillary and Lumbar Plexuses—No evidence of neuritis, but obvious myositis is present in adjacent skeletal muscle

DISCUSSION

This case was submitted to Dr W Freudenthal, who very kindly gave his opinion that the histological lesions are indistinguishable in the muscles from those in dermatomyositis, those in the skin although slight are nevertheless suggestive

A study of the literature shows that dermatomyositis not infrequently presents initially as a cutaneous disease O'Leary *et al*, reviewing 40 cases, found that in 14 œdema and cutaneous lesions ushered in the illness, while Goldman described a proven case in a man of 63 which started with a vesicular and keratotic eruption of hands and toes, muscular weakness was not manifest for fifteen months but then came on suddenly, developed extensively and terminated in death less than two months later The author's case, it will be remembered, showed minimal lesions in the muscle biopsy less than a month before death, yet at autopsy every single portion of skeletal muscle sectioned showed clearly demonstrable changes

Reviewing the muscle biopsy (taken one month before death) in retrospect it is evident that unless one is familiar with the condition there is little on which to base a correct diagnosis

However, on comparing it with a section of normal pectoral muscle it becomes apparent that certain features had either been overlooked or wrongly interpreted, *i e*

(1) Sarcolemmal nuclei appear on the whole more numerous and larger than normal

(2) Occasional muscle fibres show pale, central hyaline zones quite unlike anything seen in the normal Such fibres are often isolated, and not necessarily associated interstitial lesions

(3) The interstitial collections of mobile cells, though small, are characteristic of myositis although at this stage the adjacent muscle fibres are often showing little or no change Elements at first mistaken for nerve cells are, in point of fact, sarcoblasts

Comparing the muscle biopsy obtained during life with sections from the same removed at autopsy it thus becomes apparent that within the space of about one month a remarkable advance had taken place in the disease—if we assume that the biopsy fragment was representative of the skeletal tissue as a whole Further, it demonstrates that clinical signs may be well established when histological abnormality is relatively slight, this may account for Foots' observation that " this is becoming the bane of the surgical pathologist, as its presence is often suspected by the clinician, and its lesions are not often demonstrable in the muscle and skin sent in for pathological examination "

The surgical pathologist examining a muscle biopsy may have to distinguish this disease from certain other possibilities —(1) Weil's disease, (2) acute myositis, (3) myasthenia gravis, (4) trichiniasis, (5) poylarteritis nodosa

In the majority of cases his task will be easy if he has access to clinical details, and if he bears the following points in mind —In Weil's disease the muscular lesion is one of patchy hyaline degeneration, with a striking vacuolation of the muscle fibres, there is negligible interstitial infiltration by mobile cells (in contrast to dermatomyositis) but swelling and proliferation of sarcolemmal nuclei is an important feature

In acute myositis suppurative lesions of various sizes occasionally complicate typhoid fever or pyogenic infections, but their acute nature as well as the clinical circumstances usually facilitate diagnosis A variation on this theme is found in the focal hæmorrhagic muscular necrosis sometimes seen in acute infections, and which, when accompanied by extensive hyaline change in the fibres, is known as Zenker's degeneration, while the appearances of individual muscle fibres may resemble dermatomyositis the interstitial lesions are mainly œdema, fibrin deposition and hæmorrhage

Trichiniasis —The interstitial reaction again may resemble dermatomyositis, but the presence of larvæ and focal necrosis is distinctive Likewise, in polyarteritis nodosa the fibrinoid vascular lesions and necroses are characteristic and diagnostic

SUMMARY

(1) A case of dermatomyositis, in which the cutaneous manifestations preceded the muscular by several months, is described

(2) The autopsy findings are reported, and the histological features compared with a biopsy of muscle taken during life , marked differences in degree are noted and discussed with a view to future diagnosis during life by means of biopsy examination

The author is greatly indebted to Drs A S Hall and K M Robertson for access to the clinical data of this case

REFERENCES

Foot, N C (1945), *Pathology in Surgery*, Lippincott
Goldsman, D , *Arch Int Med* , 70, No 5
Holmes, J MacD (1942), *Brit Med Journ* , 2, 511, 1948 Nov
Lamb, J H (1944), *Journ Oklahoma State Med Assoc* , 37, No 5
O'Leary, P A *et al* (1940), *Arch Dermatol Syphilol* , 41, 1001-1019
Walinger and Lever (1949), *Arch Dermatol* , 59, No 2, 196

RETINAL CHANGES IN HYPERTENSION

By JOHN MACASKILL, M B, F R C S E, D O M S

THE changes sometimes seen in the fundus of the eye in association with raised blood pressure have attracted attention almost since the time when this region could be observed For here, as in no place else in the body, it is possible, in life, to view the finer branches of the great vascular tree and to observe any changes in the tissue they serve

The introduction of the ophthalmoscope added greatly to the knowledge of those changes and resulted in the accumulation of a large literature on them It is appropriate, therefore, this year to pay tribute to Helmholtz, who first introduced his ophthalmoscope exactly one hundred years ago Inevitably, the changes which we now associate with raised arterial tension attracted notice and in 1876 Gowers remarked on the changes in the retinal arteries in certain patients with chronic Bright's disease in whom the blood pressure was raised A few years later Gunn gave the first detailed description of those changes and all subsequent writers have recognised the accuracy of his descriptions He realised that the changes in the retinal vessels were related to hypertension and noted that they may be present when there was no evidence of kidney disease Early in this century Foster Moore elaborated, and added to, Gunn's description and correlated the retinal changes with those found elsewhere in the body He showed the relation of " arterio-sclerotic retinitis " to vascular sclerosis and distinguished the condition from these changes in the retina now recognised as the retinopathy of malignant hypertension The changes in this latter condition and their significance has formed the studies of many subsequent writers, notably Volhard, Keith and Wagener, and Fishberg

ASPECTS OF THE NORMAL FUNDUS —Before passing to a consideration of abnormal changes, it is perhaps well to consider some aspects of the normal fundus One is apt to forget, when using the electric ophthalmoscope, that a very magnified image is obtained, one of sixteen diametres in fact, and if it is remembered that the optic disc is only 1 5 mm in diameter, then the minute and often microscopic nature of many of the changes seen will be realised In this respect, too, the minute calibre of even the bigger vessels will be appreciated, something of the order of 0 25 mm or less, and there has been controversy whether they are not rightly regarded as arterioles Maximow and Bloom classify as arterioles those branches of the arterial system with a diameter of 0 3 mm or less, so that if this is accepted then the retinal vessels can be so regarded

The walls of the retinal vessels are very poorly developed and this renders them translucent, so that what is viewed as a retinal artery is indeed the blood column contained within this translucent tube

A Honyman Gillespie Lecture given 14th June 1951

CHANGES IN THE RETINAL VESSELS WITH AGE —Gowers stated, that in a retina free from local disease any marked change in the vessels might be taken as evidence of a similar change elsewhere in the body, and it is well to have in mind that sclerotic vascular changes, of which the most common cause is hypertension, occur also in other conditions such as diabetes and syphilis The changes in the retinal vessels which are said to accompany old age warrant some attention, for raised blood pressure frequently occurs in the later decades of life when the ageing process is giving rise to changes elsewhere in the body

It is within the experience of all who have the opportunity of examining many fundi that many old, sometimes very old people, have perfectly normal retinal blood vessels when viewed by the ophthalmoscope Their appearance and calibre and the arterio-venous crossings are absolutely normal Gunn, writing on the retinal vascular sclerosis which he was observing stated, " that such changes do not occur from age alone " and added that many old persons of seventy to eighty years of age have perfectly normal blood vessels Fishberg in studies with Oppenheimer found, in old individuals with extreme arterio-sclerosis of the palpable vessels but with no evidence of present or antecedent hypertension, that sclerosis of the retinal vessels was absent or minimal, while Foster Moore found normal retinal vessels in life in cases in whom, at post mortem, gross atheromatous changes of the big vessels were seen, in those cases in whom there had been no rise in blood pressure Numerous other writers have come to similar conclusions, but Pines and Duke-Elder are not so absolute in their statements and believe some slight changes in the retinal vessels do occur from age alone, but that they are " not markedly visible in the absence of hypertension "

It is difficult to believe that the retinal vessels would be immune from the changes which occur everywhere in the body from age Ballantyne, Michaelson and Heggie showed that changes in the intima could take place without any apparent change in the vessel wall seen ophthalmoscopically, the translucency was not interfered with although some alteration in the blood column was seen where the intimal changes were marked Similarly, Bridgett in 17 cases with ophthalmoscopically normal vessels found that in only 7 cases were the vessels also histologically normal

CLASSIFICATION OF THE RETINAL CHANGES IN HYPERTENSION — I have reviewed a series of unselected cases showing hypertensive changes which were seen in the eye department In some the changes were seen in the course of routine examination, in others some happening had given rise to alteration of vision which had caused the patient to seek advice, and a few were known cases of hypertension sent for opinion on the fundi All were examined in the dark room, some on several occasions over a period of some months I am indebted to Dr Trevor Kinnear for much help from the general medical aspect of the cases, and it is a pleasure to record my thanks to him Th blood pressure was recorded in all in some a re 'as availab after rest in bed for some days, but in the majority the readings are those taken in the out-patient department and on this account may be somewhat high, but as this possible error is common to all groups it hardly affects comparison between them Only cases in whom positive fundus changes were present in association with hypertension are included, so it may not be out of place to mention the many cases of low grades of arterial hypertension in which there are no changes in the retinal vessels or in the retina

Although in past years much has been learned of the clinical pattern of hypertension, the causative factors remain unknown, in consequence, classification presents a difficulty and the varied terminology which has been used gives expression to this Volhard and Fahr realised that one group, with distinctive features in the retinal vessels, followed a relatively benign course, and was compatible with fair health and moderate length of years Another group, which they called malignant hypertension, also had characteristic retinal features but ran a short and severe course ending in early death Keith, Wagener and Barker enlarged on this classification, sub-dividing each group into two to make four groups, and as the vascular changes were essentially arteriolar, they used the general term of diffuse arteriolar disease with hypertension

MODERATE ARTERIOLAR SCLEROSIS WITH HYPERTENSION —Keith, Wagener and Barker's first group is that in which there is only vascular sclerosis present with a mild degree of hypertension This shows itself by an increase in the brightness of the arterial reflex which imparts to it a burnished appearance which has been found to correspond with thickening of the media In estimating this change it must be remembered that an exaggeration of the normal reflex is being observed, and on this account the interpretation of this sign is capable of wide error For such an observation to have any value the " copper wire " appearance of the retinal vessels must be quite marked and distinct Keith, Wagener and Barker found the average age of hypertensives showing this early vascular sclerosis to be fifty-five The hypertension, they noted, can be of long duration without impairing general health, does not rise to extreme heights and is the commonest variety met with in practice I cannot speak of the length of life of the individuals in the group, but they were mainly noted in routine examination and were apparently not complaining of any great disturbance in health It is noteworthy, too, that in this group no retinal changes, or ocular complications of hypertension, were present

MARKED RETINAL ARTERIOLAR SCLEROSIS WITH HYPERTENSION —With raised blood pressure of a higher order the vascular sclerosis becomes more marked and additional changes may be seen Keith, Wagener and Barker classed such cases as Group II, and this group, they noted, was associated with a higher and more sustained hypertension, a moderate degree of wellbeing in many cases, and certain patients belonging to this group, they found, lived comfortably for many years

Changes at Arterio-venous Crossings —The increase in the sclerosis of the media shows itself by reduction in the translucency of the arterial wall, so that if the point where an artery crosses a vein is observed, not only is the vein concealed, but it appears to be separated from the artery by a small interval which corresponds to the sclerosed arterial wall seen end on

Sallmann has shown, by histological examination, that a corresponding increase in the connective tissue of the adventitia takes place, and that the artery and vein have a continuous meshwork of adventitia enfolding them at the arteriovenous crossings Increase of the adventitia in this region results in the vein becoming partially obscured near the artery, and gives the impression of it tapering on either side of it

Gunn saw in many cases of vascular sclerosis with marked hypertension other changes at the arterio-venous crossings In some, the vein on the peripheral side of an arterio-venous crossings appeared to dilate as if to form a little ampulla Gunn thought—and most people accept the view—that this resulted from mechanical obstruction to the venous backflow, but against this simple explanation is the occurrence in some cases of a similar dilatation of the vein on the other side of the crossing Whatever is the pathology giving rise to the change, there is no doubt, as Gunn pointed out, that it occurs in association with marked vascular sclerosis and considerable hypertension and is, of course, well known as Gunn's sign

Normally when a vein crosses obliquely beneath an artery the line of direction of the vein is unaltered Foster Moore drew attention to an alteration in this state in certain cases wherein a well developed degree of vascular sclerosis and hypertension was present The vein at the crossing appears to change direction and crosses the artery approximately at right angles, thereafter continuing its course It might be thought that this was merely displacement by a thickened arterial wall, but a precisely similar effect has been seen when the vein crosses superficial to the artery

All studies of the retinal changes in hypertension have shown that the changes described at the arterio-venous crossings occur in the presence of well-developed vascular sclerosis and hypertension In contrast to the change in appearance of the vessel wall which is capable of wide individual interpretation, the changes at the arterio-venous crossings are definite and positive and so form a most useful sign in the retina of vascular sclerosis and of the presence of hypertension

To underline the importance of the changes at the arterio-venous crossings I have divided up those cases which would fall into Keith, Wagener and Barker's Group II, into those with slight changes at the arterio-venous crossings and those in whom those changes were severe (Table I) It will be seen that the hypertension is markedly higher in the second group and in this group too, secondary retinal changes make their appearance and the incidence of complications becomes greater

Changes in Calibre—Apart from the periodic spasm which may occur in vessels in this group of hypertension and which will be referred to later, there is evidence that a generalised reduction in calibre due to increased tone may be present This is a very difficult observation to make unless it is extreme and requires repeated examination to be certain of its presence—for it is to be remembered that a very wide variation may be seen in the calibre of normal retinal vessels More reliable, and indeed as Foster Moore states, pathognomonic of hypertension, is the variation in vessel calibre from place to place which may be seen He believes that when this is present, a high or very high degree of hypertension exists

TABLE I

	Age		Blood Pressure			Retinal Changes	Complications	Cases
	Range	Mean	Syst	Dias	Mean			
Vascular sclerosis only	43 76	58	130 210	80 130	$\frac{161}{92}$	None	None	8
Vascular sclerosis with slight A V " changes	38 70	60	130 230	82 130	$\frac{179}{102}$	None	Venous thrombosis 2 Vaso spasm 1	7 7
Vascular sclerosis with marked " A V " changes	47 78	63	170 260	100 155	$\frac{215}{122}$	Hæmorrhages 5 ' Arterio sclerotic retinitis " 4	Arterial occlusion 4 Venous thrombosis 3 Vaso spasm 1 Optic atrophy 1	18
Acute angiospastic retinopathy	34 54	46	220 260	130 140	$\frac{247}{135}$	Retinopathy	" Amaurosis fugax ' 1	3

There is hardly space to list all the possible changes in the retinal vessels in hypertensive vascular sclerosis, as for instance pipe-stem sheathing and tortuosity of the vessels In this latter condition it is to be remembered that the very wide range of tortuosity of the retinal vessels seen in normal eyes detracts greatly from the value of such an observation

Secondary Retinal Changes—It is in the group of benign hypertension with considerably raised blood pressure and marked vascular sclerosis that the secondary changes in the retina are seen

The retinal hæmorrhages are small, sometimes so small as to require much searching to find them, and are commonly in the nerve fibre layer, on this account being often flame-shaped They are, of course, not unique to hypertension and are believed to result from an anoxia of the capillaries, the integrity of whose walls becomes impaired, allowing formed elements of the blood into the substance of the retina This explains their fine and minute nature and it is interesting that the small retinal hæmorrhages sometimes seen in anæmia are of a similar type

The combination of hard white exudates and retinal hæmorrhages was first given the name of " Arterio-sclerotic Retinitis " but it is now known that the changes are not inflammatory in nature and that the term " Retinitis " is a misnomer The hard white exudates are small collections of hyaline material in the outer molecular layer of the retina and by carefully drawn maps and painstaking observation Moore watched them disappear, leaving no trace, while others made their appearance Like the retinal hæmorrhages, they are not peculiar to hypertension, but may be seen in other conditions They have only significance, as far as hypertension is concerned, in the presence of vascular sclerosis, and have been noted to evolve in cases previously showing vascular sclerosis alone They are small in size and sparse in distribution and are ophthalmoscopically in sharp contrast to the retinal œdema and patches of soft exudate seen in malignant hypertension

Varied opinions have been expressed about these retinal changes They were shown to belong to the picture of hypertension and not to general arterio-sclerosis, and Foster Moore and Gunn showed them to be part of the severe vascular sclerosis of the retinal vessels with hypertension of the benign sort as opposed to the acute angiospastic retinal changes of malignant hypertension The former writer thought they were incidental to the vascular sclerosis, and it is now generally held that they are in themselves of no special significance and that the severe vascular sclerosis which they accompany is the important guide to the severity of the hypertension present

Retinal hæmorrhages were seen in 5 cases and, as mentioned, they were small and sparse in distribution and occurred in the presence of well-marked vascular sclerosis and hypertension It will be seen that they were present in cases which had average blood pressure very similar to the average values found in those cases which showed marked sclerosis alone, and tend to show that they are probably no different from the cases in this group

Retinal "Complications" of Hypertensive Arteriolar Sclerosis — Any group of cases, such as the present, seen in an eye department inevitably includes a disproportionate number of what might be termed the ocular complications of the vascular sclerosis of hypertension, and they are of interest for the light they throw on the pathological changes of the disease It is noteworthy that their occurrence is confined to the group in which there is a more severe degree of vascular sclerosis, as shown by the arterio-venous crossing changes, and moreover they are most frequent where those changes are most severe

It is generally believed that tonic spasm of arterioles is responsible for the attenuation of the retinal arteries in hypertensive cases, and I have referred to the difficulty in assessing change in calibre of these vessels A considerable reduction in calibre can occur without giving rise to any impairment of the visual function of the retina , however, periods of more intense vascular spasm occur, which are severe enough to interfere with retinal function, so that the patient experiences some loss of vision Two such cases were seen in the group examined, and some details of one may be instructive

The first was a married woman of thirty-eight, with a fair degree of retinal vascular sclerosis and a resting blood pressure of 170/110 For five years she had experienced transient loss of vision in one eye, the vision remaining away for about four minutes on each occasion She was seen first when the vision in the eye had remained away for six hours, and at the end of that time some returned, but the lower visual field, bounded by the horizontal meridian, remained completely blind There was a reduction in calibre in the retinal vessels by comparison with those in the other eye, and the upper temporal division of the artery showed, some way from the disc, a localised area of acute spasm No apparent change in this was brought about by rest and intra-venous hexamethonium, although some recovery in the visual field took place in the following days Some months later there was no sign of the area of spasm although a small dense visual field defect was present She was free from disturbance for some months, but recently she came again because of loss of part of the visual field, and on this occasion one of her retinal arteries, or more properly arterioles, showed 12 to 15 small areas of spasm so that the artery had the appearance of a string of sausages Rest in bed for a day or two caused most to disappear, but one remained which has been present for two weeks On this occasion, too, hexamethonium had no ophthalmoscopically visible effect

This is a case in which the increase in arteriolar tone, suspected of playing an essential role in hypertension, became at times so severe as to give rise to functional upset in the tissue supplied by the vessels and finally complete cessation of function in a small region

Five cases of thrombosis of the central retinal vein or one of its tributaries were seen Coats and others are in agreement that this occurs most frequently in the presence of retinal vascular sclerosis, and Moore found a marked degree of hypertension in 40 of 61 consecutive cases of those which he examined The 5 cases in the series seen by me would be included in Group II of Keith, Wagener and Barker's grouping

There is hardly space to deal with the other complications apart from noting their incidence in that group of so-called benign hypertension which is associated with marked arteriolar sclerosis and a correspondingly high degree of hypertension The vascular changes, the occasional incidental retinal changes and those I have classed as complications occurred in the type of hypertension classed by Volhard and Fahr as benign and by Keith, Wagener and Barker in their second group

ACUTE ANGIOSPASTIC RETINOPATHY —The relationship of kidney disease to hypertension is essentially outwith the scope of a lecture by an ophthalmologist and appears indeed to be the subject of much speculation It was early recognised that severe retinal changes were seen in association with chronic glomerulo-nephritis These changes were gross œdema of the optic discs, exudates of a particular type into the retina and very marked constriction of the retinal vessels

Because of the association with kidney disease and albuminuria, the name of albuminuric retinitis or neuro-retinitis was given to include the changes at the nerve head Allbutt, however, was the first to realise that a similar state of affairs could exist in the retina, without, for a time at least, evidence of severe kidney disease or albuminuria, and attention became directed to the invariable feature of severe hypertension which all cases showed Fishberg made similar observations, showing that in all patients, without exception, with the changes now called malignant hypertensive retinopathy, the blood pressure was high and in the few in whom this was not the case the pressure had dropped because of cardiac weakness or the process was regressing Volhard and Keith, Wagener and Kernohan showed, too, that this type of retinal change could occur in cases in which there was no clinically demonstrable renal change and in whom post mortem revealed only essentially vascular lesions of the kidneys The unsuitability of the term albuminuric retinitis was further evident when Volhard showed that the changes were related to the spastic changes in the vessels and suggested the term acute angiospastic retinopathy The changes were seen in patients who were already severely ill, or usually became so, in contrast to the more benign form of hypertension whose retinal changes have been discussed Volhard and Fahr classed this as malignant hypertension and, as mentioned already, Keith, Wagener and Barker subdivided this to form their groups three and four of hypertension

All surveys of such cases, showing the changes of malignant hypertensive retinopathy, indicate its frequency in a much younger age group than that in which the retinal changes of benign hypertension are seen Keith, Wagener and Barker, who have the biggest series I could find, are typical, the average age in their groups three and four being forty-two and forty respectively In the cases under review I found the average age to be forty-six

Earlier writers believed the fundus picture varied in those cases of malignant hypertension without antecedent kidney disease and those with Fishberg, who has studied this matter in detail, believes that there are many instances in which ophthalmoscopic differentiation between the malignant phase of a hypertension previously benign and that associated with a glomerulo-nephritis is impossible The œdematous changes may be present in addition to the retinal vascular sclerosis of a hypertension previously benign, or the vascular sclerosis may be so slight that the œdematous changes occur in a fundus whose vessels are apparently normal except for their extreme attenuation in calibre by spasm The same has been found to be true of those cases of malignant hypertensive retinopathy in whom antecedent kidney disease is recognised, previous vascular sclerosis may or may not be present

On looking at a fundus, showing the changes of malignant hypertension retinopathy, one is struck by the œdematous appearance of the tissues, the retinal texture is altered and the reflex of the ophthalmoscope light is different , lines of apparent tension may make their appearance, giving the retina a watery, œdematous look In the loose tissues around the disc this is especially seen, where the

TURNER'S SYNDROME IN A MALE INFANT

By THEODORE JAMES

(From the Duchess of York Hospital for Babies, Manchester)

IN 1938 Turner described a syndrome which he had observed in 7 unrelated females whose ages ranged from fifteen to twenty-two years He published the syndrome under the heading "A Syndrome of Infantilism, Congenital Webbed Neck and Cubitus Valgus" This triad occurs often enough to give it a distinctiveness The webbing of the neck, which varied from slight to marked in Turner's cases, gave the neck only an apparent shortness for there was no skeletal fusion or absence of cervical vertebræ This apparent shortening had an accompanying low hair-line on the back of the neck which had no noticeable limitation of movement There was no mental deficiency A constant finding, but variable in degree, was a cubitus valgus, or an increase in the carrying angle of the elbows, and all 7 cases presented osseous and sexual retardation of development which Turner thought comparable with that of hypopituitarism Roentgen study of the bones did not show any gross deviation from the normal Treatment with pituitary growth hormones was without effect, but there followed a definite genital development after anterior pituitary gonadotropic hormone in 2 cases

Since Turner's descriptive paper which did much to establish the syndrome it is being more frequently recognised, and more than 100 cases have appeared in the literature on both sides of the Atlantic However, the first case of the syndrome in a male to be reported was diagnosed in 1943 by Flavell His case was aged twenty-one years and was serving satisfactorily in the Royal Air Force The intelligence was normal but the physique was below average There was quite marked webbing of the neck but no real shortening A cubitus valgus was present and a kyphoscoliosis associated with a prominence of the sternum There was also a third degree bilateral claw-foot The beard was scanty, there was no axillary hair and the pubic hair had a female distribution The penis was of normal size but the testes were hypoplastic, despite which erection and emission were normal In addition there was a failure of union of the fifth cervical neural arch

The second case report of the syndrome occurring in a male was by Dorff, Appelman and Liveson (1948) Their patient was only three years old There was webbing of the neck, shortness of stature, an enlarged head and genital underdevelopment Mental development had been average since birth, and the usual "milestones" had been passed at an average rate of progress A cubitus valgus was suspected (*sic*) There was no hair on the body but much fatty subcutaneous tissue of the breast, accompanying a deformity of the front of the thorax A murmur was audible all over the precordium Bilateral pes planus and an overriding toe on the right foot were present Roentgenologic examination revealed a spina bifida bone defect between the last lumbar and upper sacral segments There was some delay in the development of the carpal bones *There was no perceptible urinary excretion of gonadotropins on 2 assays*, that is, there was no increase in the follicle-stimulating-hormone (FSH), which is contrary to the usual finding in females

In the same year (1948) Greenblatt and Nieburg reported 2 cases of Turner's syndrome, one of these being a coloured male thirty years of age, whose height and weight corresponded with the upper limits of an eleven-year-old child He showed webbing of the neck, a marked carrying angle (cubitus valgus), slight talipes varus, poor muscular development, moderately poor beard, small testes with atrophy of the left The penis was described as " very large " and the illustration accompanying the case report leaves no doubt about this paradoxical and confusing feature There was no evidence of heart disease or coarctation of the aorta A biopsy of the right testis revealed a hypoplasia of the seminiferous tubules, azoospermia and a relative increase in the interstitial cells Two urinary 17-ketosteroid estimations were at the low level of normal range, and serum gonadotropin assays showed no increase These hormone assays did not help to explain the huge phallus

In 1949 Reforzo-Membrives, Trabucco and Escardo gave a very detailed case report of the syndrome in an Argentinian boy aged ten and a quarter years This case report also included the findings of a testicular biopsy The child's height was below average, the abdomen was large, the skin smooth and there were many nævi on forehead, nose, neck and thorax This latter finding is not uncommon in the female but this case of Reforzo-Membrives *et al* is the only case so far reported to show this skin anomaly in a male Their case also showed a kypho-scoliosis, cubitus valgus, a largish head and an impression of bilateral epicanthus The neck was webbed The thorax was deformed and the heart had a systolic murmur at the apex The penis was small and the scrotum small with few folds The testes were small also but in the scrotum and were normal to palpation There was hypotonia of muscles and flat-feet The mental level was close to subnormal The 17-ketosteroids were less than the normal average and no FSH was detectable on repeated examinations

The fifth and latest case report of Turner's syndrome in a male that I have been able to collect, is one reported by Cunningham and Harley in 1951 Their case was aged seven years The stature was short, the head relatively large, there were flat-feet, pterygium colli, underdeveloped penis, cryptorchidism There was a bilateral slight ptosis and moderate cubitus valgus Intelligence was at the low level of normal The 17-ketosteroids in the urine were estimated to be 1 1 mg per twenty-four hours when assayed, and the gonadotropins 6 mouse units

The following is the youngest male case to be reported

CASE REPORT

M H , No 27/269, a male infant was aged two years and three months when he was referred for a second opinion by request of the parents The chief complaint was one of failure to grow physically and mentally

Family History —Both parents were alive, young and well There was one sibling, a sister, aged four years, who was living and well in every way The family background was non-contributory The mother had had only two pregnancies

Past History —From the mother's account of her pregnancy wher she was carrying M H there was good reason to believe that she suffered from a polyhydramnios, but she contracted no illnesses during that time She felt well in herself and brought this pregnancy, her second, to term The patient was born at home, and although the birth itself took place normally the baby's first cry was not heard until several hours later, and in the night of the birthday the neonate vomited what, to the mother, appeared to be swallowed amniotic fluid This vomiting caused the baby to choke, and the mother added the remark that fluid seemed to come from every orifice of the baby's body The birth weight was 8 lb 6 oz (3 8 kg)

There was difficulty in feeding the patient from the very beginning, both breast and artificial feeding were unsuccessful From the age of three months the patient attended the out-patient department of a hospital in its home-town because of this feeding difficulty, and continued to attend there for twelve months, but not much progress in management of the feeding of the patient could be made It was about this time that congenital disease of the heart in M H was first diagnosed During this time, also, it had become borne in upon both parents that there was evidence of physical and mental retardation manifesting in their second child M H was eighteen months old before he could sit up unaided, but his first teeth erupted at six months of age and the set of milk teeth was completed in the usual time There was no distortion or evidence of disease of these teeth which were, however, rather widely spaced

The patient had not contracted any illness, nor suffered any accident or operation No vaccination or immunisation procedures had been carried out on him

When M H was fifteen months old the family transferred their domicile and sought further advice about their son's failure to thrive A diagnosis of primary amentia associated with congenital disease of the heart was made and the parents advised accordingly A halfhearted trial with thyroid extract was attempted but not persevered with when no rapid response was evoked

Adequate nutritional intake by the patient still remained a subsidiary problem for the parents when he was brought to this hospital

Physical Examination —The patient was a white male child whose age was two years and three months His temperature, respiration and pulse were normal His length was 80 0 cm (32 in), sitting height 53 7 cm (21 5 in), sitting height index $\left(\frac{\text{sitting height}}{\text{full length}} \times 100\right)$ 67 per cent , head circumference 46 2 cm (18 5 in), chest circumference 52 5 cm (21 in), abdominal circumference 42 5 cm (17 in), and weight 11 kg (24 lb 2 oz)

General Appearance —The first impression was that the child was well nourished, but closer inspection revealed a marked flabbiness of the subcutaneous tissue The child was quite placid until examined, when he whined and resented the examination continuously, but otherwise he was in no distress His colour was fair and his cheeks pink A strong suspicion rested that the patient presented a syndrome , the facies were neither mongoloid nor cretinoid, but mental retardation was evident The mouth tended to remain open and the tongue to protrude and the child persistently scratched his skin

Skin —This was cool and without blemishes of any kind but was remarkably dry although it was capable of perspiration Except for the dorsal aspect of the trunk, however, where there was a fine lanugo-like hair the skin was hairless Skin elasticity was greater than normal By bending the neck laterally to either side it was easy to bring out the folds of a latent pterygium colli, and traction of the skin over the mastoid processes produced a striking webbing of the neck (see Fig 1)

The Lymph Nodes showed no abnormality

Head —Although the head appeared relatively large when compared with the rest of the body its circumference (46 2 cm) was less than average (49 cm) The fontanelles were closed There was no bossing or cranio-tabes of the skull The hair of the scalp was plentiful, fair, of fine texture, and the occipital hairline came low The skull was brachycephalic in its configuration

Eyes —These were not prominent, there was no suggestion of hypertelorism, mongoloid slant, epicanthic folds or ptosis of the eyelids The pupils were equal, round, of moderate size and reacted to light There was no nystagmus nor strabismus and ocular movements were normal Funduscopy was normal and the only abnormality determined was a considerably short optic axis

The pinnæ of the *Ears* were not deformed but were set rather low on the head

The Nose presented a flattened bridge which was a little broader than average, but there was no nasal discharge and the airways were patent

The Mouth had a complete set of slightly stained, rather widely spaced milk teeth which were otherwise normal in appearance The lips were full, the tongue, with several deep grooves, tended to protrude with salivation, but was of normal size , the gums, mucous membranes, palate, fauces and tonsils and pharynx were normal to inspection

The Neck was not short and was freely mobile It was broad from side to side, but pterygium was not apparent without adopting the manœuvre previously described

The Chest —There was some depression of the lower sternum but no signs of scurvy or rickets There was no precordial bulging but there was an excess of mammary fatty subcutaneous tissue (see Fig 2)

The Lungs were normal to percussion and auscultation

The Heart —No impulse was visible nor thrill palpable, nor was there clinical evidence of enlargement, but on auscultation there was a grade III systolic bruit audible all over the precordium but not between the scapulæ The radial pulses were equal in tension and rhythm and the femoral pulses readily palpable It was not practicable to measure the blood pressure

The Abdomen —The spleen tip was palpable, but not the liver edge, and no other masses were palpable except costive fæces in the large gut There was evident some muscular weakness of the anterior abdominal wall in the right inguinal region

The Genitalia —The penis was small (2 5 × 1 cm) with a complete prepuce enclosing the glans, but the external urethral orifice was placed so as to present a slight degree of hypospadias The scrotum, although rugose and dusky was rudimentary and empty Both testes were of normal size and shape and of normal consistency but situate just over the external inguinal rings from where they could, by manual traction, be pulled into the scrotal sac When they were released from this position, however, they would fly back to their former position and at times disappear altogether down the inguinal canals

The Spine in the sitting position showed a mild degree of scoliosis which could be attributed to a slight deficiency of muscle tissue of the erector spinæ muscle of the right side This deficiency was palpable Flexibility of the spine was full in all directions The coccyx was clinically abbreviated, the tip being 3 cm from the posterior margin of the anus There was a deep dermal sinus overlying the coccyx but without any apparent attachment to the deeper structures From this there was no exudation

The Upper Extremities —These were of normal length and conformation The range of active and passive movements did not appear lessened, but muscle power was not good and all joints showed an abnormal increase in flexibility, extensibility and other associated movements (see Fig 3) There was no obvious cubitus valgus but there was an abnormal laxity of the joints so that it was easy enough to place both elbows in a marked degree of cubitus valgus passively The fingers tapered and there was a slight webbing of the middle

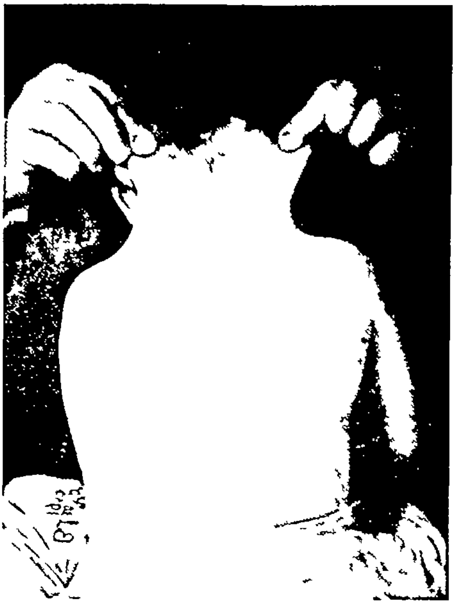

FIG 1 —This shows the webbing of the neck produced by slight traction on the skin over the mastoid processes

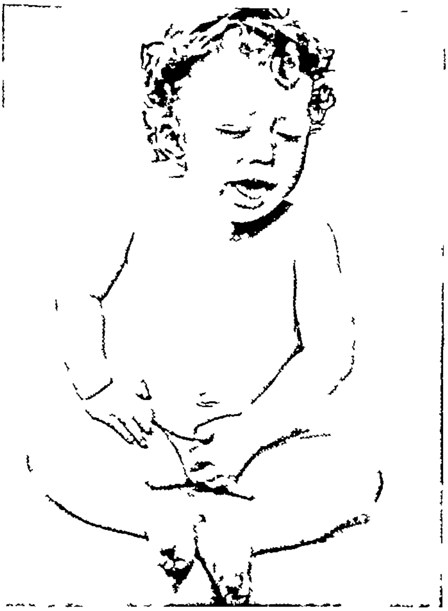

FIG 2 —The depression of the sternum, excess of fatty subcutaneous tissue and cramping of the toes are obvious

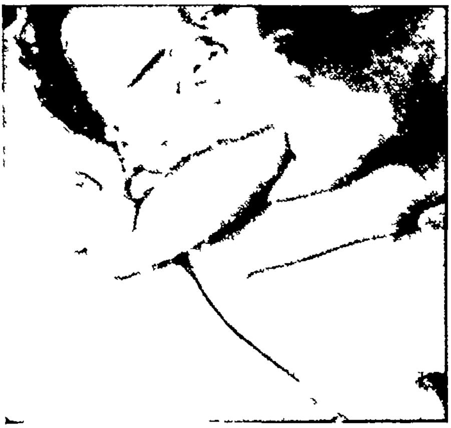

FIG 3 —Illustrative of the excessive range of joint movement common to all joints

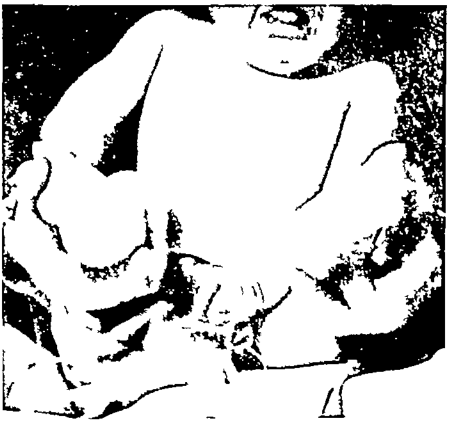

FIG 4 —The hypotonia readily permitted the demonstration of the potential flat foot

and ring fingers bilaterally and a slight medial curving of each index finger

The Lower Extremities likewise, showed abnormal degrees of mobility of all joints and tended to be rather spindle-shaped but otherwise of usual configuration, except for the feet where the toes had a cramped appearance On the right foot the great toe and fifth toe were almost in juxtaposition underneath and on the left foot there was an underriding of the fourth toe which also brought this toe close to the great toe—both feet appeared as though they had been laterally compressed There was a severe potential degree of flat foot (see Fig 4)

Nervous System —The mentality appeared dull and the sensorium clouded but there was no doubt that the patient was aware of his environment However, there was no pattern of neurophysiological integration exhibited All the deep tendon reflexes, despite the generalised hypotonia, were readily elicited and showed no asymmetry of responses and there were no abnormal nervous reflex mechanisms

Laboratory Data —The hæmoglobin was 84 per cent , erythrocytes, 4 24 million, white blood cells 7000 with a differential count of polymorphonuclear leukocytes, 40 per cent , lymphocytes, 54 per cent eosinophils, 3 per cent , monocytes, 2 per cent , and Turk cells, 1 per cent The routine urinalysis was normal and there was no detectable phenylpyruvic acid in the urine The serum inorganic phosphorus was 5 9 mg per cent , the serum chloride 646 mg per cent as NaCl, serum calcium 8 5 mg per cent , serum potassium 19 8 mg per cent alkaline phosphatase, 16 2 K A units, serum cholesterol 155 mg per cent

A fasting blood sugar level was 85 mg per cent and a glucose tolerance test (using about 15 gm of glucose, the patient resented the glucose) gave 100 mg per cent after half an hour, 80 mg per cent after one hour and 75 mg per cent after two hours

On 25th to 26th November 1951, urinary excretion of 17-ketosteroids and gonadotropins were assayed 17 ketosteroids 3 6 mg per litre or 1 6 mg per twenty-four hours and the gonadotropins were 8 mouse units per litre or 3 5 mouse units per twenty-four hours

The Wassermann reaction and the Kahn precipitation test gave negative results and the tuberculin skin test (1 1000 dilution) was also negative An electrocardiographic tracing did not point to any cardiac abnormality A radiological skeletal survey did not show any changes from normal configuration except for some evidence of osteoporosis in the long bones of the lower extremities

COMMENT

It is proper to give consideration to the extreme youth of this patient in evaluating the clinical features present in this case At a first glance Turner's triad is not prominent, but careful examination disclosed not only a retardation of general physical and genital development but the readily demonstrable presence of the webbing of the neck and potential cubitus valgus The latter condition when fully manifested is dependent upon growth of the medial epicondyle of the humerus, and until osseous growth, however slow, does take place the cubitus valgus will remain latent but allowed for by the laxity of the ligamentous joint structures Probably, this was what Dorff *et al* implied when they used the word " suspected " in connection with cubitus valgus in their young patient of three years

Beyond Turner's triad, however, this case demonstrated quite a number of associated clinical features, such as the hypotonia, excessive range of movement of all joints, digital anomalies, almost hairless skin, congenital defects of the heart and a mental retardation which might not be synonymous with mental deficiency

The hormone assays were confirmatory of the syndrome

DISCUSSION

There is good evidence that this syndrome had not gone unnoticed before 1938 when it was so prominently brought to the attention of endocrinologists and gynæcologists by Turner

Ullrich (1950) stated that, from developmental and phenotypical points of view " the asymmetrical form of the Status Bonnevie-Ullrich corresponds entirely with the anomalous complex of *my*—mice engendered in embryos of the Bagg-Little mouse by the mechanism of wandering cerebro-spinal fluid blebs discovered by Bonnevie The typical complex of abnormalities with pterygium colli is, as the symmetrical form of the Status Bonnevie-Ullrich, identical with the syndrome of infantilism, webbed neck and cubitus valgus described by Turner in 1938 In this complex of developmental abnormalities the symmetrical distribution of all the defects makes the syndrome incompatible with the wandering bleb mechanism, which, also, cannot satisfactorily explain the infantilism connected with it, and the obvious gynæcotropy Embryonic fœtal swellings of the skin, however, which in this syndrome are probably of autochthonous origin, must account for the greater part of the abnormalities of the Turner syndrome just as in the asymmetrical condition "

Funke (cited by Rossi and Caflisch, 1951) in 1902 was the first to describe a case of webbed neck and sexual infantilism so closely allied, if not identical, with Turner's syndrome

Rossi, Caflisch and Angst (1950) in order to show the aetiology and pathogenesis of the multiple malformations grouped under the eponyms of Ehlers-Danlos syndrome, Turner's syndrome, the Status Bonnevie-Ullrich, and arthromyodysplasia congenita (multiple congenital articular rigidities) emphasised the analogy of these affections with those observed by Bonnevie in the rat In this latter connection there was a display of microphotographs demonstrating an " area membranacea superior " in man which might possibly be the equivalent of the anterior foramen of Weed through which the cerebro-spinal fluid, in the rodent, passed into the subcutaneous tissue One of the conclusions to which these authors came as a result of a clinical study of 4 cases of the Ehlers-Danlos syndrome, 20 of pterygium colli and 9 of arthromyodysplasia congenita in their own experience, and a further study of other cases in the literature, was that Turner's syndrome is identical with the Bonnevie-Ullrich syndrome

The lack of terminological exactitude for the condition under discussion justifies, perhaps, an extension of the eponymous designation to " the Bonnevie-Ullrich-Turner syndrome " which does draw attention to the degrees of variation possible for the syndrome

Rossi and Caflisch (1951) reviewed 177 cases in the literature and 20 of their own cases showing multiple malformations associated with pterygium formation, and they suggested that the classical picture should be referred to as the " pterygium syndrome " They observed that certain malformations occur regularly in most of the cases and allow a sub-classification into 5 main groups the bilateral Ullrich syndrome, dystrophia brevicolli congenita (Nielsen), pterygo-nuchal infantilism (Turner), unilateral Ullrich syndrome, and congenital pterygo-arthromyodysplasia However, the only deduction they make with any feeling of certainty is the presence of a hereditary factor determining the anomaly These authors grouped together all conditions which manifested a pterygium whether of neck, axilla, knee or fingers and whether in the typical or abortive form

Albright, Smith and Fraser (1942) in a paper which contained descriptions of 11 cases of a syndrome characterised by primary ovarian insufficiency and decreased stature, went into some detail and tabulated 11 points which their cases brought out for consideration These 11 points included references to the short stature, infantile genitalia, scanty pubic hair, retardation of bone age, a constant increase of FSH, a lower than average normal of 17-ketosteroids, response to œstrin therapy, the insulin tolerance test, and associated other congenital anomalies These authors were inclined to regard Turner's similar series of cases as a sub-form of the syndrome they were describing Among the associated congenital anomalies they found webbing of the neck, and coarctation of the aorta especially frequent

Ezes, writing in Algiers in 1949 mentioned 6 cases of Turner's syndrome in females which had appeared in the French literature He noted the not uncommon presence of pigmented nævi which Reforzo-Membrives *et al* found so conspicuous in their male child patient, a shortness of the fourth metacarpal, a slight epicanthus, bilateral genu valgum, coarctation of the aorta, and absence of the spheno-occipital suture He had found recorded in the literature, autopsy evidence of absent mesenteric vascular arcades, a constant hypoplasia or aplasia of ovaries and hypomorphosis of the adrenal cortices

In the female the syndrome *almost* always includes an increase in the pituitary gonadotropins which accompanies the ovarian insufficiency The features of dwarfism, increased urinary gonadotropins, decreased 17-ketosteroids, are not absolutely constant findings, and as Reforzo-Membrives *et al* say, this lack of uniformity in the elements of the syndrome raises the problem of pathogenesis and weakens the contention of Albright *et al* that the absence of ovarian œstrogens diminishes the stimulus for the production of androgens by the suprarenal cortex This decrease shows as a low value for the 17-ketosteroids, which might be the reason for the defective growth It is difficult to reconcile this theory with the existence of the syndrome of " rudimentary ovaries " in patients with a normal or even increased 17-ketosteroid level (Del Castillo, cited by Reforzo-Membrives *et al*) Most authors are inclined to believe that the association of " rudimentary ovaries " with defective growth is due to genetic factors (Ezes) , Dorff *et al* believe a slight alteration in the hypophysis could account for delay, retardation, or stunting of growth, but because of their failure to prove the presence of hypophyseal gonadotropins in the urine of their patient, they could not attribute to a diminished function of the testes the same importance which is given to the ovaries in the pathogenesis of the syndrome, which was the reason for the differential diagnosis between their case and hypophyseal dwarfism not being obvious and a fundamental difference between cases of " rudimentary ovaries " and their case, that is, a lack of the hypophyseal gonadotropin in the urine of their patient after repeated search They suggested two explanations for this discrepancy either a primary testicular insufficiency without an increase in hypophyseal gonadotropins or, a gonadal insufficiency which could be the result of a congenital hypophyseal disturbance, perhaps a predominant deficiency of the gonadotropins leaving the other hypophyseal functions less affected Dorff *et al* also regarded the absence of urinary excretion of gonadotropins in their case as being compatible with the age (three years) of their patient and the production of hormone as being likely to take place at the age of puberty Reforzo-Membrives *et al* give some support to this opinion They too, found no FSH in their case on repeated examination and the 17-ketosteroids were less than the average normal, and they cite Talbot when they state that available data indicate that gonadotropins are not detectable in the urine of normal boys before the twelfth year of life

These observations give considerable significance to the finding of gonadotropins in my case , 8 mouse units per litre or 3 5 mouse units per twenty-four hours represents a marked increase in this hypophyseal hormone and the determination of 3 6 mg per litre or 1 6 mg per twenty-four hours for the 17-ketosteroids, a marked decrease This tallies well with the endocrinological assays which have been shown to be usual in the female with the syndrome These hormonal findings in my case positively exclude it from those of hypophyseal origin

The subject of this report not only presented Turner's triad but also several other outstanding clinical features There were a deformity of the chest, a postural scoliosis (due to a deficiency of the right erector spinæ muscle), a congenital defect of the heart, a marked increase of joint movement beyond the normal range and a mental retardation or deficiency accompanying an unusual peculiarity of the facies

Rossi and Caflisch (1951) make a statement of much import which demands agreement on the identities of the 5 syndromes which at intervals have been reported in the literature and which they have grouped together Should their thesis find general acceptance, then the impression prevailing at the present time that Turner's syndrome in the male is a great rarity will fall away and there no longer will be a call for the special mention which it now receives

They write as follows " Nous n'avons jusqu'ici fait etat que du sexe feminin parce que le syndrome de Turner a ete decrit presque exclusivement chez les femmes Cependant une analyse minutieuse de la litterature nous a permis de noter la présence de ce syndrome egalement chez l'homme En effet, nous avons trouve 13 fois une cryptorchidie bilaterale ou unilaterale avec atrophie de l'autre testicule ou plus rarement d'autres malformations genitales, comme l'hypospadie ou le scrotum bipartit Nous avons fait 3 observations analogues chez nos enfants dont les testicules etaient insuffisamment developpes tandis que le penis etait normal " Such a statement negates the care which has been taken by writers who have studied cases of Turner's syndrome, to exclude such conditions as the Klippel-Feil alone, or the dystrophia brevicolli congenita of Nielsen which *includes* the Klippel-Feil structural anomaly of the cervical vertebræ

An observation which I have not met with in the relevant literature, but which has quite strikingly entered my experience, is the extraordinary similarity of the facies of the 3 infant cases of Turner's syndrome which I have seen The other two infant cases were females and the diagnosis for the second female case was suggested by its likeness to the first case, already diagnosed, and my male infant so closely resembled the other two that Turner's syndrome was immediately advanced as a working diagnosis

SUMMARY

The few male cases of Turner's syndrome which have appeared in the literature as such, are reviewed

Another male case of the syndrome, the youngest that I know of, is presented

A discussion gives consideration to different interpretations of the syndrome in the female These have been propounded by different authors, and where the syndrome in a male has shown a discrepancy from the syndrome as it occurs in the female, the responsible author's comment has been added

Notice is drawn to an opinion expressed by the authors of one paper in which it is stated that the widely held understanding that Turner's syndrome occurs almost exclusively in females, is in error

I wish here to thank Mr G Ward, the hospital photographer, for the photographic illustrations

REFERENCES

Albright, F , Smith, P H , and Fraser, R (1942), *Amer Journ Med Sci* , 204, 625

Cunningham, G C , and Harley, J F (1951), *Journ Pediat* , 38, 738

Dorff, G B , Appelman, D H , and Liveson, A (1948), *Arch Pediat* , 65, 555

Ezes, H (1949), *Gynéc et Obstét* , 42, 390

Flavell, G (1943), *Brit Journ Surg* , 31, 150

Funke (cit Rossi and Caflisch, 1951)

Greenblatt, R B , and Nieburg, H E (1948), *Journ Clin Endocrinol* , 8, 993

Reforzo-Membrives, J , Trabucco, A , and Escardo, F (1949), *Journ Clin Endocrinol* , 9, 1333

Rossi, E , and Caflisch, A (1951), *Helvet Pædiat Acta* , 6, 119

Rossi, E , Caflisch, A , and Angst, H (1950), Scientific Exhibition, Sixth International Congress of Pædiatrics, Zurich

Turner, H H (1938), *Endocrinol* , 23, 566

Ullrich, O (1950), Scientific Exhibition, Sixth International Congress of Pædiatrics, Zurich

Varney, R F , Kenyon, A I , and Koch, F C (1942), *Journ Clin Endocrinol* , 2, 137

OBITUARY

SIR DAVID WALLACE, K B E , C M G , LL D , F R C S E

THE oldest of Edinburgh surgeons passed away at his Edinburgh residence on 21st April within three months of his ninetieth birthday David Wallace, who came of a Fife family, was born in 1862, son of David Wallace of Balgrummo His school education was at Dollar Academy, from which he entered Edinburgh University, and graduated M B , C M in 1884 During the next year he was house surgeon in Edinburgh Royal Infirmary to Professor John Chiene, and house physician to Professor John Wyllie With one exception, all his fellow residents are now dead From the outset he aimed at a surgical career, and by 1886 he had obtained the qualification of M R C S Eng , and a year later that of F R C S E In 1892 he was appointed assistant surgeon in Edinburgh Royal Infirmary, where for some years he was assistant to Professor Chiene, to whom for a time he was also private assistant Previously he had followed the frequent Edinburgh surgical custom of holding a demonstratorship in the University Department of Anatomy In due course he was in charge of wards as surgeon from 1908 to 1923 for the usual period of 15 years, after which he became consulting surgeon After leaving the Infirmary he was for many years visiting surgeon to Longmore and Liberton Hospitals for Incurables , and he took a prominent part in the management of the Princess Margaret Rose Orthopædic Hospital at Fairmilehead

Sir David was involved in military surgery in the South African War, as he was in charge of the expeditionary Edinburgh Hospital, of which, in association with Mr George Chiene, he wrote the Report , he was mentioned in despatches, received the medal and clasp, and was appointed C M G In 1908, on the formation of the Territorial Force, he, along with the more senior surgical members of the Infirmary, was included in the staff of the 2nd Scottish General Hospital, and they were mobilised in August 1914 He had, however, played an important part in the formation of an Edinburgh branch of the Red Cross Society in 1908 , and indeed he was ultimately secretary or chairman for over thirty years It was rightly considered in the first war that his services would be of greatest value in this sphere, and he was appointed Commissioner of the Red Cross for the south-eastern district of Scotland This was a much more difficult position than an ordinary army command Among other duties there fell to him the organisation and supervision of the numerous Red Cross convalescent homes, many of which were large mansions generously offered by their owners, and he was very successful in meeting the wishes of the owners where possible and in showing firmness where essential, without giving offence For his services he was appointed C B E in 1918 and K B E in 1920 , and he retired from the Territorial Army with the rank of Brevet Lieutenant-Colonel

Sir David was an example of the best type of surgical specialist, an excellent general surgeon with special interest in one branch of surgery In his case this was urology, in which, encouraged in his earlier years by Professor Chiene, he was one of the pioneers in Edinburgh and an accepted authority , and this was recognised abroad by his election to the French Association of Urology

Among his other honours he was President of the Royal College of Surgeons of Edinburgh from 1921 to 1923, and was its senior resident Fellow at the time of his death He had been examiner in surgery and clinical surgery for the University of Aberdeen, was a Deputy-Lieutenant of the City of Edinburgh, and in 1930 the University of Edinburgh conferred upon him the honorary degree of LL D He contributed many articles on surgical subjects to medical journals

Sir David was a successful teacher in his systematic class in the School of Medicine and clinically in the Royal Infirmary, where he always had a large class He was clear and definite in his teaching, kindly to patients, possessed the valuable gift of a retentive memory for names and faces, and was popular with colleagues, students and patients He was a good administrator, for he had a logical mind which led him to definite, often dogmatic, decisions He would always listen closely and courteously to opposing arguments, but it was not easy to persuade him to change an opinion to which his logical thought had led him

Sir David married a daughter of the late Sir Thomas Clouston, the eminent specialist in mental diseases, by whom he is survived Lady Wallace, like her husband, is an excellent administrator, especially well known in relation to the Victoria League and the Queen's Institute of District Nursing, and in 1946 she received the honour of C B E He is also survived by his two sons, neither of whom has followed the medical profession

Sir David Wallace had outlived almost all his actual contemporaries, and during the last few years failing health had withdrawn him from most of his surgical interests, but he had intimate friendships with many men younger than himself, to whom his death is a real personal grief

NOTE

Royal College of Physicians of Edinburgh

AT a Quarterly Meeting of the College held on Tuesday, 6th May 1952, the President, Dr W A Alexander, in the Chair, the following were elected Fellows of the College —Ronald Foote Robertson, M B EDIN , John Taylor Randolph Russell, M D , EDIN

The following were elected Members of the College —Gostha Bihari Sinha, M B CALC , Sunder Balse, M B BOMB , Sanatkumar Hiralal Shah, M B BOMB , Graham Francis Hall, M B N Z , Michael John Bailey, M B CAPE TOWN , Sutcliffe Ruttle, M D BELF , Deb Prasanna Basu, M B CALC , Bal Sitaram Kulkarni, M B OSMANIA , Neol Myddleton Mann, M D CANTAB , Douglas Telfer Kay, M B EDIN , Oliver Gordon Jones, M D LEEDS , Walter Bolliger, M B SYDNEY , Andrew Macfarlane, M B EDIN , Nathaniel Kemsley Pein, M B WITWATERSRAND , William Ian Forsythe, M D BELF , William Dawson Hamilton Conacher, M B GLASG , Anilkant Dulerai Desai, M B BOMB , Zahur Hussain Nurullah Kadri, M D BOMB , Shanti Narain Mathur, M B OSMANIA , Robert Arthur Kershaw, M B MANC , Bermeshwer Prasad, M B PATNA , George Stewart Kilpatrick, M B EDIN , Roger John Connolly, M B SYDNEY , Kenneth Lamonte Stuart, M B BELF , John Alexander McLeod, M B OTAGO , Balbir Singh Khaira, M B CALC

NEW BOOKS

Psychosomatic Gynecology By WILLIAM S KROGER, M D , and S CHARLES FREED, M D Pp xvii+503 London W B Saunders 1951 Price 40s

This volume stresses the importance of emotional factors in the etiology of obstetrical and gynæcological disorders, and indicates how the individual's personality may be assessed and treated From an extensive bibliography, ranging mostly over the last thirty years, the authors have collected many varying viewpoints To these they have added their personal opinions and supported them by illustrative case histories

The authors are aware of the controversial and often speculative nature of some of the material presented, and constantly admit that the psychiatric approach is limited by such incompleteness of fundamental knowledge Yet the practical importance of this subject is recognised, and in this volume will be found an interesting attempt to define the present stage of its development and therapeutic value

The reviewer feels that making each chapter an essay, complete in itself, has resulted in tedious repetition A more closely knit presentation and condensation would enhance another edition

Fellowship Examination Papers, 1947-1951, *For the Diplomas of the Royal College of Surgeons, Edinburgh* Pp 50 Edinburgh E & S Livingstone 1951 Price 5s 6d net

Racing enthusiasts, football pool addicts, and examination candidates study form This is the " form book " for the Fellowship Aspirants should find it useful but should always beware of the dark horse

The Diagnosis and Treatment of Intrathoracic New Growths By MAURICE DAVIDSON, M A , D M , B CH (OXON), F R C P Pp vi+260, with 170 illustrations London Oxford University Press 1951 Price 42s net

In this book Dr Maurice Davidson writes in a readable and pleasant way about intrathoracic new growths, illustrating his subject by extensive case histories and numerous radiographs The book suffers from two misfortunes It apparently went to press too late to include any mention of the recent British and American work demonstrating the association between heavy tobacco-smoking and carcinoma of the bronchus Again, probably owing to delay in publication, the international nomenclature of the bronchi, which has been recently agreed, has had to be included only as an appended table The diagram of the normal bronchi, shown in Fig 1, is presumably a tracing of a bronchogram and gives the mistaken impression that there are lateral communications between the bronchi this should be altered in later editions The chapter by Professor Smithers on radiotherapy is excellent but might with advantage have been twice as long , that by Mr O S Tubbs on operative treatment is an admirable summary, reflecting a wide personal experience and containing much of interest to the physician

Hygiene, Infectious Diseases and Dietetics By DENNIS H GEFFEN, M D , D P H , and SUSAN TRACY, M R C S , L R C P , D P H Pp viii+276 London Longmans, Green & Co 1951 Price 9s 6d net

Two London teachers have written this book to cover the syllabus laid down for student nurses by the General Nursing Council The authors hope that it will also be useful to students of social welfare These aims are fulfilled well, and doctors called upon to lecture to nurses on these subjects will also find it valuable The book covers practical problems which arise in Great Britain, but will be of little use to nurses in the tropics

Summary of Legislation and Directory of Organisations for the Care of the Physically Handicapped Compiled by the Central Council for the Care of Cripples Pp xiii+139 London Heinemann 1951 Price 5s 6d net

The title is sufficiently comprehensive to make the book attractive to those who seek guidance on that subject and they will not be disappointed The explanatory notes on the various Acts and organisations are concise and well written

Surgical Practice of the Lahey Clinic By Members of the Staff of Lahey Clinic, Boston Pp xiv+1014, with 784 illustrations on 509 figures London W B Saunders 1951 Price 75s

This volume presents the practice of the Lahey Clinic, and while it is not intended to cover the whole field of surgery, the extensive practice of the Clinic provides material for a considerable number of its aspects Naturally the treatment of thyroid disease has a large place, and the remainder of the book deals with the surgery of the œsophagus, lungs and heart , the stomach and duodenum , the small intestine, colon, sigmoid and rectum , the biliary tract , the spleen, adrenal gland and pancreas , the breast , the pelvis , the bones and joints , the brain, spinal cord and nerves , and anæsthesia Dr Lahey points out in his introduction that many of the operative procedures have become standardised, and that he finds this useful both in the training of young surgeons and in the care of the patient Whether the principle be accepted or not, the book contains the fruits of a large experience which has been dealt with by Dr Lahey and his colleagues in an exceedingly thoughtful manner Some of the letterpress and some of the illustrations are repeated more than once from paper to paper (which should be unnecessary for standardised techniques), but this criticism apart, the volume will well repay perusal by even experienced surgeons whether or not they agree with the views and the procedures it describes

NEW EDITIONS

Treatment by Manipulation By H JACKSON BURROWS, M D, F R C S, F R A C S, and W D COLTART, M B, F R C S Second Edition Pp 80, with 29 illustrations London Eyre and Spottiswoode 1951 Price 12s 6d net

Manipulation forms a small but important part of orthopædic treatment This is a small book in true perspective, not seeking like some to over emphasise its subject Indications, hazards and methods are clearly described, but it is impossible to teach technique by printed word or still photograph For all its clarity this book does not achieve the impossible

Applied Pharmacology By A J CLARK Eighth Edition, revised by ANDREW WILSON, M D, PH D, F R F P S, and H O SCHILD, M D, PH D, D SC Pp xii+691, with 120 illustrations London J & A Churchill 1952 Price 37s 6d net

Ten years have passed since A J Clark's death a year after the publication of the seventh edition of his well-known textbook In view of the enormous advances in the subject in the interval the authors have had to revise the book completely and add new chapters The fundamental character of the book has been maintained, and, as before, pharmacology is presented on a solid foundation of physiology and pathology The only real change is the exclusive use of the metric system in the dosage of all preparations The authors are to be congratulated on maintaining the high standard of former editions, and the new " Clark " should prove as popular with students and practitioners alike as the original

Diseases of the Nose, Throat and Ear By I SIMSON HALL, M B, CH B, F R C P E, F R C S E Fifth Edition Pp xii+463, with 8 coloured plates and 82 illustrations Edinburgh E & S Livingstone 1952 Price 18s net

The early appearance of a further edition of this textbook is an indication of its well-merited popularity Designed for the practitioner and student, its general features and size are unchanged It has been brought thoroughly up to date, notably on the subjects of the physiology of the nose, the employment of antibiotics in acute otitis media and the treatment of Meniere's disease A special section is devoted to the use of the antibiotics The insertion of alternative metric dosage in the formulæ is a useful addition The price of this edition has increased only by 3s and it continues to be an admirable volume

A Synopsis of Hygiene (Jameson and Parkinson) By L ROBERTS, M D, M R C P, D P H, with the assistance of KATHLEEN M SHAW, M B E Tenth Edition Pp viii+891 London J & A Churchill 1952 Price 42s net

This " synopsis " first appeared thirty two years ago and rapidly established itself as a standard textbook for D P H students and a reference work for the M O H 's office On Brigadier Parkinson's retirement, Dr Roberts, the M O H of Sheffield takes over the editorship, assisted by Kathleen Shaw of the London School of Hygiene and Topical Medicine The scope and style of the book remains essentially unchanged, and the new edition is a workmanlike mixture of the old hygiene and the new social science and legislation that go to make modern public health This edition presents an up to date account of public health practice in England to day The account of the great work of the World Health Organisation is, however, crammed into less than two pages Could the next edition have a more imaginative account of W H O 's aims and achievements ?

Warwick and Tunstall's First Aid to the Injured and Sick Edited by A P GORHAM, M V, M R C S, L R C P, D A Nineteenth Edition Pp 278, with 288 figures Bristol John Wright & Sons 1952 Price 6s 6d

Dr Gorham has brought this old established guide up to date in accordance with modern practice The first eighty pages are devoted to an elementary account of anatomy and physiology essential for the first aider, and the remainder deals with various aspects of the subject, wounds, hæmorrhage, fractures, asphyxia, poisoning, unconsciousness and so forth Descriptive details are more elaborate than in the average book of this sort and the copious illustrations are helpful and entirely adequate One of the best manuals of its kind

BOOKS RECEIVED

CROSSE, V MARY, O B E, M D (LOND), D P H, M M S A, S (OBSTET), R C O G The Premature Baby Third Edition (*J & A Churchill, Ltd, London*)	16s net
FISHER, JAMES T, M D, and HAWLEY, LOWELL S The Diary of a Psychiatrist (*Medical Publications Ltd, London*)	16s net
GREENHILL, J P, M D Surgical Gynecology (*The Year Book Publishers Inc, Chicago, U S A*)	65s net
GULLAN, M A, S R N Theory and Practice of Nursing Sixth Edition (*H K Lewis & Co Ltd, London*)	18s net
HARDY, JAMES D, M D, F A C S Surgery and the endocrine System (*W B Saunders Company, London*)	25s
HARTWELL, JONATHAN L Survey of Compounds which have been Tested for Carcinogenic Activity Second Edition (*United States Government Printing Office, U S A*)	$4 25
ISHIHARA, S, M D Tests for Colour Blindness Tenth Revised Edition (*H K Lewis & Co Ltd, London*)	75s net
JOHNSTONE, R W, C B E, M A, M D, HON LL D William Smellie (*E & S Livingstone Ltd, Edinburgh*)	20s net
KORNITZER, MARGARET Child Adoption in the Modern World (*Putnam, London*)	16s net
Edited by LEVY, ROBERT L, M D Disorders of the Heart and Circulation (*Thomas Nelson & Son, Edinburgh*)	91s 6d net
LOVATT EVANS, SIR CHARLES Principles of Human Physiology Eleventh Edition (*J & A Churchill Ltd, London*)	52s 6d net
MANSON BAHR, SIR PHILIP H, C M G, D S O, M A, M D, D T M, and H (CANTAB), F R C P (LOND) Synopsis of Tropical Medicine Second Edition (*Cassell & Company Ltd, London*)	15s net
Edited by MONCRIEFF, ALAN, M D, F R C P A Textbook of the Nursing and Diseases of Sick Children Fifth Edition (*H K Lewis & Co Ltd, London*)	37s 6d net
PEEL, ALBERT A FITZGERALD, M A, D M (OXON), F R F P S (G) Diseases of the Heart and Circulation Second Edition (*Oxford University Press, London*)	35s net
Edited by PLUNKETT, RICHARD J, M D, and HAYDEN, ADALINE C, R R L Standard Nomenclature of Diseases and Operations Fourth Edition (*H K Lewis & Co Ltd, London*)	60s net
SIMPSON, KEITH, M D (LOND) Forensic Medicine (*Edward Arnold & Co, London*)	21s net
WALSHE, F M R, M D, D SC, F R S Diseases of the Nervous System Seventh Edition (*E & S Livingstone Ltd, Edinburgh*)	24s net
WOLFF, WERNER The Threshold of the Abnormal (*Medical Publications Ltd, London*)	30s net
WOLSTENHOLME, G E W, O B E, M A, M B, B CH Ciba Foundation Colloquia on Endocrinology Volume I (*J & A Churchill Ltd, London*)	30s net
S F A Catalogue of Medical Films (*Harvey & Blyth, London*)	15s net

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ACUTE APPENDICITIS

By I E W GILMOUR, F R C S E, and A G R LOWDON, O B E, F R C S E

(*From the Department of Surgery, University of Edinburgh*)

RECENT articles on appendicitis have drawn attention to the improvement in the last ten to fifteen years in the figures for morbidity and for mortality In a review of 1265 cases treated in the Presbyterian Hospital of New York in the five-year period 1944-48, Schullinger (1950) reported a mortality of 0 94 per cent, compared with a mortality of 3 18 per cent in the whole period 1916-49 Cotter and Gebbie (1948) quote figures from Christchurch Hospital, New Zealand, in which, from 1942-47, 2489 cases of appendicitis were treated with a mortality of 0 76 per cent, in the years 1937-42, a series of 2122 cases from the same hospital showed a mortality of 1 7 per cent Wakeley and Childs (1950) reported 217 appendicectomies performed without a death from February 1947 to August 1949, their article is prefaced by information procured by the Registrar-General for England and Wales, which confirms the fall in mortality in recent years

Many factors are responsible for this improvement, earlier diagnosis, the introduction of chemotherapeutic drugs, improved anæsthesia and the more liberal use of intravenous fluids have all contributed towards the reduction in mortality This review is an attempt to assess the relative values of these factors, and to find out how further improvement may be obtained, by comparing the results in two series of cases of acute appendicitis treated in the Royal Infirmary of Edinburgh during the two periods 1930-31 and 1948-50 respectively

SELECTION OF CASES

The years 1930-31 and 1948-50 were chosen for this comparison because the advantages of modern anæsthesia, intravenous therapy and antibiotic drugs became established in the intervening period The cases in 1930-31 were taken from the wards of Sir David Wilkie and Sir John Fraser, and the cases in 1948-50 were taken from the same wards under the charge of Sir James Learmonth

The case records of all patients diagnosed as having appendicitis or treated by appendicectomy were reviewed and care was taken to eliminate from both series all cases in which the diagnosis of acute appendicitis was not adequately established by operative findings or clinical progress the results of this selection are of incidental interest as evidence of changing surgical opinions and practice

Series A 1930-31 —From all the cases diagnosed as appendicitis in these years a small number of patients under twelve years of age was excluded because in the second period all such patients were admitted to the Royal Hospital for Sick Children The total number of cases reviewed was 745 , 170 of these were interval appendicectomies or cases of "chronic appendicitis," and 40, diagnosed as acute appendicitis, had a normal appendix at operation The remaining 535 were accepted as cases of acute appendicitis

Series B 1948-50 —Consecutive cases from the beginning of 1948 were examined and selected in the same way until an equal total of cases of acute appendicitis was reached , thus all cases in 1948, 1949 and about nine months of 1950 were reviewed The smaller number of cases in these later years is probably accounted for by the fact that more emergency surgery is being carried out in the peripheral hospitals in the city and surrounding district The total number of cases was 681 Of these, 30 were interval or "chronic" cases and in 116 the appendix was normal the remaining 535 were accepted as cases of acute appendicitis

The change in numbers of chronic and normal appendices is of interest The smaller number of cases of "chronic appendicitis" in the later period is explained by the present reluctance to make this diagnosis The increase in the numbers of "normal" appendices removed is due to the more frequent recognition at operation of non-specific mesenteric adenitis

Further analysis is confined to the 535 acute cases in each period In both series the operations were performed by a number of different surgeons who were, with few exceptions, of the registrar grade

ANALYSIS OF CASES AND RESULTS

The mortality in Series A was 4 9 per cent , in Series B 1 1 per cent

Classification —For simplicity, four types of acute appendicitis have been distinguished —

(1) Simple acute appendix inflamed, but not perforated
(2) Perforated, with local peritonitis early localised peritoneal involvement
(3) Perforated with general peritonitis inflammation spreading or generalised in the peritoneal cavity
(4) Abscess localised intraperitoneal collection of pus from an appendicular lesion

An analysis of the total numbers and mortality rate in each type of appendicitis is given in Table I

The numbers for each type of appendicitis show a striking similarity Comparison of the two series shows that the mortality has been reduced in all types of appendicitis, most strikingly in cases of abscess, and that in Series B fatal cases were confined to the group with perforated appendices

TABLE I

Acute Appendicitis Classification and Mortality

Type of Appendicitis	Series A 1930 31			Series B 1948 50		
	Total	Deaths	Per cent Mortality	Total	Deaths	Per cent Mortality
Simple acute	392	4	1 0	403	0	0
Perforated local peritonitis	88	4	4 5	76	2	2 6
Perforated general peritonitis	36	13	36 1	35	4	11 4
Abscess	19	5	26 3	21	0	0
Total	535	26	4 9	535	6	1 1

Age in Relation to Mortality—The distribution of cases in age groups by decades is shown in Table II The number of patients under forty years of age was 440 (82 2 per cent) in Series A, and 429 (80 2 per cent) in Series B

TABLE II

Age Distribution and Mortality

Age in Years	Series A 1930 31		Series B 1948 50	
	Total	Deaths	Total	Deaths
12 19	195	5	203	
20 29	167	6	135	1
30 39	78	2	91	
40-49	40	3	43	
50 59	30	5	39	2
60 69	24	5	13	1
70 79	1		11	2
Totals	535	26	535	6

In both series the mortality was higher in the older age groups The mortality in patients over forty years of age was 12 4 per cent in Series A and 4 7 per cent in Series B In patients under forty years of age the mortality was 3 4 per cent in Series A and 0 2 per cent in Series B

Sex in Relation to Mortality—In both series there were more males than females Table III shows that in both series the incidence of perforation and the mortality were higher in males

Duration of Illness before Admission in Relation to Mortality—Comparison of the two series in respect of duration of illness before admission to hospital shows that there has been no important change (Table IV)

TABLE III

Sex Distribution, Incidence of Perforation and Mortality

Sex	Series A 1930 31					Series B 1948 50				
	Total	Perforated		Deaths		Total	Perforated		Deaths	
		Number	Per cent	Number	Per cent		Number	Per cent	Number	Per cent
Males	291	81	27 8	13	4 5	280	83	29 6	4	1 4
Females	244	62	25 4	9	3 7	255	49	19 2	2	0 8

TABLE IV

The Relation of Mortality to Duration of Illness before Admission

Series A 1930 31					Series B 1948 50				
Number of Days before Admission	Number of Cases	Number with Perforated Appendix	Deaths	Per cent Mortality	Number of Days before Admission	Number of Cases	Number with Perforated Appendix	Deaths	Per cent Mortality
1	300	36	13	3 3	1	300	36	3	0 7
2	96	36			2	104	42		
3	45	17	13	9 3	3	53	25	3	2 3
4	25	18			4	25	11		
Over 4	69	36			Over 4	53	18		
Total	535	143	26	4 9	Total	535	132	6	1 1

The principal interest of this comparison appears to lie in the numbers of late cases with perforation on admission The number of patients with perforation of the appendix and a history of four or more days' illness was 54 in Series A and 29 in Series B This is a significant difference and might indicate that perforation is occurring earlier, but more probably shows that practitioners are recognising the development of peritonitis sooner

It is noteworthy that perforation of the appendix occurred within the first twenty-four hours in 36 (6 7 per cent) cases in Series A and in an identical number in Series B , of these 9 (1 7 per cent) in Series A and 14 (2 6 per cent) in Series B had general peritonitis

In both series the mortality rises with delay in admission to hospital

TREATMENT

The following aspects of the management of the cases under review merit consideration the effect of purgation before admission to hospital, and changes in the methods of treatment employed with particular reference to drainage, chemotherapy, intravenous infusion, gastric aspiration, the management of abscess, and anæsthesia

Catharsis—Of the 1070 patients in the review, 99 had taken purgatives Of these, 49 (49 5 per cent) had perforated appendices Of the remaining 971 patients, 226 (23 3 per cent) were admitted with perforated appendices

The estimate of the number of patients taking purgatives is based on the case records The total is therefore the accountable minimum and it is probable that in both series there were unrecorded cases of purgation

Drainage—The most striking change in technique is the recent tendency to omit peritoneal drainage when the appendix is perforated In Series A the peritoneum was drained in all cases of perforated appendix In Series B the practice was not uniform six cases of abscess resolved under conservative treatment, in the remaining 126 cases with perforated appendix the peritoneum was drained in 75, the wound alone was drained in 32, and in 19 the wound was closed without drainage

The results of peritoneal drainage, wound drainage and non-drainage may be estimated by comparing the incidence of wound infection and residual intraperitoneal abscess in the two series "Wound infection" is taken to include all cases where healing was delayed by prolonged discharge, abscess formation or disruption of the wound The use of chemotherapeutic drugs in 92 per cent of cases of perforated appendix in Series B complicates the interpretation of the results In addition, the total figures are dependent upon the accuracy of the case notes the number of wound infections recorded is probably too small, particularly in respect of Series A in which the notes are less detailed than in Series B

The incidence of wound infection in cases of perforated appendicitis was smaller in Series B than in Series A (Table V)

In Series B peritoneal drainage and wound drainage gave the same proportion of infected wounds but the incidence of delay in wound-healing was higher when the wound was closed without any drainage

The wound was left open after suture of the peritoneum in 28 cases in Series A and in 18 in Series B Secondary closure of these wounds was followed by uninterrupted healing in 10 (36 per cent) in Series A and in 14 (78 per cent) in Series B The higher proportion of successful delayed sutures in Series B is doubtless ascribable largely to chemotherapy (all these patients received antibiotics and some also sulphonamides) but the outcome may have been influenced also by the omission of drainage of the peritoneal cavity in most of the cases in the later series

There is no important difference in the numbers of residual intraperitoneal abscesses in the two series, there being nine in Series A and seven in Series B In the latter series there were 126 cases of perforated appendicitis treated by operation, in the 75 cases with intraperitoneal drainage there were three cases of residual abscess, in the 51 cases in which the peritoneal cavity was not drained there were four cases of residual abscess All the cases of residual abscess in Series B occurred in patients who had received penicillin in full doses in the immediate post-operative period

TABLE V

Drainage of Wounds and Incidence of Wound Infection in Cases of Perforated Appendicitis

SERIES A 1930 31
143 Cases of Perforated Appendicitis

	Number of Cases	Per cent of Total	Number with Wound Infection	Per cent.
Peritoneal cavity drained	143	100	66	46 2

SERIES B 1948 50
126 * Cases of Perforated Appendicitis

	Number of Cases	Per cent of Total	Number with Wound Infection	Per cent
Peritoneal cavity drained	75	59 5	26	
Wound drained	32	25 4	11	
No drainage	19	15 1	8	
Total	126 *	100 0	45	35 7

* Excludes 6 cases of appendix abscess treated conservatively

Chemotherapy —In Series B, 43 2 per cent of all cases were given chemotherapeutic drugs Analysis of the numbers and dosage in each type of appendicitis is given in Table VI Of the patients receiving chemotherapy, 95 6 per cent were given penicillin alone or penicillin with sulpha drugs Streptomycin was given to 14 patients, alone

TABLE VI

SERIES B 1945-50

Number of Cases Receiving Chemotherapy and Average Dose in Each Type of Appendicitis

Type of Appendicitis	Number of Cases	Number Receiving Chemotherapy	Per cent of Total	Penicillin Average Total Dose mega	Sulpha Average Total Dose g	Streptomycin Average Total Dose g
Simple acute	403	117	29 0	2 6	32 0	3 9
Perforated—						
Local peritonitis	76	58	76 3	4 2	16 0	4 0
General peritonitis	35	35	100 0	6 2	25 0	9 2
Abscess	21	21	100 0	4 0	30 0	14 0
All cases	535	231	43 2	4 3	25 8	7 8

in nine, with penicillin in four and with penicillin and aureomycin in one

In 23 cases penicillin or sulphonamide powder was dusted into the wound or peritoneal cavity

In perforated appendicitis the usual dose of penicillin was 100,000 units four-hourly for eight days

Intravenous Infusions —The notable changes in the use of intravenous infusions in Series B as compared with Series A are —

(1) Infusions were given more frequently in the later period, seven patients in Series A and 33 in Series B received intravenous infusions All these patients had perforation of the appendix except two with simple acute appendicitis in Series B who received intravenous therapy to treat specific complications (mechanical obstruction and ileus associated with pregnancy)

(2) Infusions were given earlier in the later period, in Series A 2 out of 7, and in Series B 26 out of 33, received intravenous infusions in the immediate post-operative period

(3) Blood was used more liberally in the later period, it was given to 3 cases in Series A and to 20 in Series B In the former, one pint was given to each of 3 patients on the second, fourth and twenty-ninth days respectively In the first two instances it was given to combat a deterioration in condition following drainage of a pelvic abscess, and in the third it was given to a patient with empyema which developed after appendicectomy for general peritonitis

In Series B, of the 20 patients who received blood, 16 (11 general peritonitis, 2 local peritonitis, 3 abscess) were given the blood immediately after operation Eight were given one pint and eight two pints Of the remaining 4 cases, one was given blood for secondary hæmorrhage, one for mechanical obstruction and two for ileus

(4) Subcutaneous and rectal administration of fluid was not employed in Series B, in Series A, subcutaneous and rectal infusions were given to 8 and 2 patients respectively, in addition to the 7 patients who received intravenous infusions

Gastric and Intestinal Aspiration —Post-operative gastric or intestinal aspiration was not employed in Series A In Series B, gastric aspiration was employed in 13 cases, and in one case intestinal suction with a Miller-Abbott tube was used successfully to treat mechanical obstruction due to pelvic abscess developing on the seventh day after removal of a perforated appendix with local peritonitis

Post-operative gastric aspiration was instituted in 7 of the 13 cases (6 general peritonitis, one regional ileitis with associated acute appendicitis) as a prophylactic measure in anticipation of paralytic ileus Six of these patients made an uneventful recovery one died and was found at autopsy to have a carcinoma of the tail of the pancreas with extensive metastases in the liver Six patients had gastric aspiration as part of the treatment of complications (two mechanical obstruction, four ileus) and of these two died, both from paralytic ileus

In all but two of the 14 cases intravenous therapy was combined with gastric aspiration

Treatment of Abscess—There were 19 cases of abscess in Series A and of these five died, out of 21 in Series B there were no deaths

Sixteen of the 19 cases of abscess in Series A were treated by operation on the day of admission The peritoneum was drained in each case In 3 cases appendicectomy was also performed, it is notable that in two of these there was technical difficulty in removing the appendix and that both these patients subsequently died of complications In 3 patients operation was delayed owing to doubt about the diagnosis until the fourth, eighth and tenth days respectively Two of these patients died The fifth death was due to inhalation of vomitus during anæsthesia

Of the 21 cases of abscess in Series B, 13 were treated by operation on the day of admission and 8 were treated conservatively Of the 13 treated by immediate operation, one had the abscess drained per rectum and the others were drained through abdominal incisions made over the mass In 7 cases the appendix was removed at the time of drainage

In two of the 8 cases treated conservatively, the abscesses failed to resolve and were later drained on the sixth and tenth days respectively after admission In the remaining six the abscess resolved and the patients were discharged from hospital to return later for interval appendicectomy

Anæsthesia—Comparison between the anæsthetic agents used in the two series shows that, in general, ether and chloroform have given place to pentothal and cyclopropane There has undoubtedly been a greatly improved standard of anæsthesia which has made the surgeon's task easier Respiratory complications have been slightly reduced In Series A one patient died under anæsthesia, this death was attributed to inspiration of vomitus in a case of ileus, failure to aspirate the stomach pre-operatively was an important contributory factor

LENGTH OF STAY IN HOSPITAL

The average length of stay in hospital for all cases has been reduced from 20 3 to 13 8 days The reduction is greatest in cases of perforated appendix with local peritonitis and in those with abscess, but it is also materially reduced in simple acute and general peritonitis cases (Table VII)

This cannot be attributed wholly to improved methods of treatment The number of beds in convalescent homes has been greatly increased since 1931 and many more patients who would otherwise have remained in the Royal Infirmary were transferred for convalescence before being sent home None the less, the shorter stay in hospital is also related to a reduced number of post-operative complications in Series B

COMPLICATIONS

Wound infection and residual intraperitoneal abscess have already been discussed in relation to drainage of perforated appendices

Respiratory complications more severe than mild bronchitis occurred in 25 patients in Series A and in 14 in Series B The figures are too small to be significant and the limitations of the available records must be emphasised Nevertheless, respiratory complications did not have an important bearing on the mortality in either series Of the deaths directly attributable to pulmonary conditions, there were in Series A one fatal case of bronchopneumonia and one case of terminal empyema , in Series B, one patient, admitted with severe bilateral pulmonary tuberculosis, died from the pulmonary infection on the sixteenth post-operative day

TABLE VII

Length of Stay in Hospital

Type of Appendicitis	Series A 1930 31 Days Average	Series B 1948 50 Days Average
Simple acute	11 9	7 7
Perforated—		
Local peritonitis	20 2	12 4
General peritonitis	21 8	15 7
Abscess	27 3	19 3
All cases	20 3	13 8

There were no fatal cases of pulmonary embolus In Series A two cases are recorded in which sudden pain in the chest occurred with fever and a friction rub pulmonary embolus was not confirmed In Series B, 6 cases received anticoagulants , all these had pain and swelling in the calf and in two there were also mild pulmonary signs

Paralytic ileus developed in 19 patients in Series A and of these 16 died , in Series B, 5 patients had established ileus and of these 2 died Thus the incidence and mortality of this complication have been materially reduced Of the 16 patients in Series A who died with ileus 11 had uncontrolled peritonitis, but in 5 the ileus was not associated with severe peritonitis and appeared to be the principal cause of death In Series B both the fatal cases had ileus without severe peritonitis The treatment of ileus in Series A consisted of pituitrin, purgatives and repeated enemata Enterostomy was performed in 7 patients and all died Nine received intravenous, subcutaneous or rectal salines, but the infusions were small in amount and haphazard in their administration In Series B ileus was treated by gastric aspiration and intravenous infusions together with the chemotherapy which had been given to all these patients from the immediate post-operative period

DISCUSSION

The recent reduction in mortality and morbidity in acute appendicitis is confirmed in this series

The factor of earlier diagnosis and treatment in hospital has been stressed by other writers, particularly in the United States of America Slattery *et al* (1950) found that a greater number of patients were presenting themselves in the early stage of the disease Darling and McIver (1950) and Tashiro and Zinniger (1946) also lay emphasis on this factor In our series it appears, as has been noted, that there has been less delay in referring to hospital patients with peritonitis, but that there is still room for improvement is evident from the fact that the proportion of patients with peritonitis is not much less in the later series It is significant that in Series B all the deaths occurred in patients in whom the appendix had perforated before operation The importance of early diagnosis and early treatment is thus again emphasised

There are, however, a proportion of patients who are found to have general peritonitis when admitted on the first day of illness In Moloney's series (1950) the figure was 5 per cent In this series the figures are somewhat lower 1 7 per cent in Series A and 2 6 per cent in Series B

The importance of catharsis in producing perforation is widely held (Nuttall, 1947) On the other hand, Brown (1951) suggested that perforation is in part attributable to the delay involved in waiting to see the effect of purgation and not to the purgation itself In this series, the higher incidence of perforation in patients who were recorded as having taken purgatives confirms the belief that avoidance of purgation in doubtful cases of appendicitis would reduce the numbers of perforated appendices

With regard to operating technique, the main point of interest lies in the question of changing practice in drainage, particularly the omission of peritoneal drainage in some cases of perforated appendix in the later series It is unfortunate that no definite conclusion about the effect of omitting peritoneal drainage can be drawn from our results Among the patients with peritonitis receiving chemotherapy the incidence of residual abscess has been slightly higher in those in whom the peritoneum was not drained

The practice of leaving the wound widely open, as advocated by Wilkie (1931), has given good results in Series B The choice of this technique was probably determined partly by the views of the surgeon, but was confined to cases where the infective contamination of the wound layers occurred It appears that in these circumstances a closed peritoneum and an open wound with the help of chemotherapy give a good prospect of rapid healing after delayed closure

Comparison of the two series in respect of the incidence of residual intraperitoneal abscess shows that there has been no significant reduction of this complication While this is at first sight disappointing in view of the benefits expected from chemotherapy, it is doubtless explained by the fact that some of the patients whose lives have been saved by chemotherapy have in the course of recovery developed a " localisation abscess "

The reduced incidence and mortality of persistent ileus in the later series is one of the striking features of the comparison The reduced incidence must be attributed largely to chemotherapy, though the use of intravenous fluids and gastric suction may have contributed to the reduction in mortality One of the recent patients with severe ileus appeared to benefit from the administration of potassium intravenously , perhaps growing appreciation of the dangers of potassium deficiency will lead to further improvement in the results of treatment of ileus

The importance of restoration of depleted blood volume in cases of general peritonitis has been emphasised by Theron and Wilson (1949) In Series B, one to two pints of blood were given to each of 16 cases of general peritonitis in the immediate post-operative period, and clinical impressions from this small number of cases suggest that blood transfusion in the early stage of the post-operative period is of great value

In the treatment of abscess, there is no evidence for or against the value of expectant treatment The influence of chemotherapy in controlling infection is again the one single important factor which distinguishes the treatment in the two series, and to it the credit must be given for the striking reduction of mortality in cases of appendix abscess

Some satisfaction that the mortality of acute appendicitis has been materially reduced in the last twenty years is fully justified, but there is no excuse for complacency It is evident that further reduction of the morbidity and mortality should be obtainable by earlier diagnosis, avoidance of purgation, improvements in the control of fluid and electrolyte balance, and the perfection of operating technique That the advent of sulphonamides and the antibiotics has been a great help in the treatment of the condition should be no more than a challenge to use these drugs, and their successors, more effectively

There has been a tendency in the past to employ the antibiotics rather indiscriminately The prophylactic administration of chemotherapy in cases of simple acute appendicitis, for example, is probably undesirable In Series B of our cases 117 patients with simple appendicitis received penicillin or sulphonamides, and in only 18 of these were the drugs given to treat specific complications In at least one case an unexplained post-operative fever abated only after penicillin was stopped Pulaski (1948) has expressed concern about the injudicious use of antibiotics and states, " There is a general tendency to institute chemotherapy or antibiotic therapy without regard to the fundamental principle of surgical management "

On the other hand, when infection has passed through the appendix wall to involve the peritoneum, chemotherapy should be immediate and adequate The difficulty arises that this treatment must be started before infecting organisms have been identified and their sensitivities determined Theoretically penicillin is not ideal because many of the organisms are relatively insensitive to it, but clinical experience (such as the series we have reported) and experimental evidence (Fauley *et al* , 1944) leave no doubt that it is of value

In bacteriological cultures from 65 of the cases with peritonitis in our series, 50 per cent of the organisms identified were *Escherichia coli* and 25 per cent were streptococci about half of which were enterococci Thus over 60 per cent of the organisms were relatively insensitive to penicillin It has been suggested by Crile (1946) and other workers that although *E coli* organisms predominate in mixed peritoneal infections the chief offenders are the gram-positive cocci It may be presumed that the value of penicillin depends mainly on its effect on bacteria which are fully sensitive to the drug None the less, higher concentrations of penicillin are likely to bring increasing numbers of the relatively insensitive organisms under control, and when penicillin is used in these cases it should be given in large doses

Streptomycin was used in a few of our cases, usually in combination with penicillin , while the clinical impression was favourable the numbers are too small to provide evidence Work by Bloemers and Kempf (1950) has suggested that penicillin and streptomycin used together may have additive effect in controlling experimental *E coli* peritoneal infections in mice It seems probable that streptomycin should at present be employed along with penicillin in the immediate treatment of cases with peritonitis When the sensitivities of the infecting organisms have been determined the treatment can be altered if necessary The tendency for organisms to become resistant to streptomycin is well known , the initial dose should be adequate to eliminate any sensitive organisms rapidly and it is probably useless to continue streptomycin therapy for more than two or three days It has been our practice to give a first injection of 1 g of streptomycin followed by ½ g every eight hours, but even larger doses for a short period might be profitable

Antibiotics which are to be used in the immediate post-operative period to treat perforated appendicitis must be given parenterally and the newer drugs (chloramphenicol, aureomycin, terramycin) have the disadvantage that their administration by injection must be intravenous Their other advantages may, however, be shown to outweigh this consideration and controlled studies of their effects will be desirable when the preparations for injection become generally available in this country Some reports are already available from America Wright *et al* (1951), in a review of 235 consecutive cases of peritonitis, consider that aureomycin is the antibiotic of choice Pulaski and Shaeffer (1951) consider that streptomycin and penicillin used together, and terramycin or aureomycin used singly, are effective agents

Summary

One thousand and seventy cases of acute appendicitis are reviewed with comparison of results in the periods 1930-31 and 1948-50 The overall mortality has fallen from 4 9 per cent to 1 1 per cent The factors responsible for this improvement are considered

It is concluded that further reduction of morbidity and mortality should be obtained by earlier diagnosis, avoidance of purgation, improvements in the control of fluid and electrolyte balance, the perfection of operating technique and progress in antibiotic therapy

REFERENCES

Bloemers, H W , and Kempf, J E (1950), *Ann Surg* , 132, 235
Brown, F R (1951), *Brit Med Journ* , 1, 136
Cotter, W M , and Gebbie, I (1948), *New Zealand Med Journ* , 47, 225
Crile, G (1946), *Amer Journ Surg* , 72, 859
Darling, A P , and McIver, M A (1950), *Ann Surg* , 131, 307
Fauley, G B , Duggan, T L , Stormont, R T , and Pfeiffer, C C (1944), *Journ Amer Med Assoc* , 126, 1132
Moloney, G E , Russell, W T , and Wilson, D C (1950), *Brit Journ Surg* , 38, 52
Nuttall, H C W (1947), *Brit Surg Practice*, 1, 318 London Butterworth & Co Ltd
Pulaski, E J , and Shaeffer, J R (1951), *Surg Gynec Obstet* , *Internat Abs Surg* , 93, 13
Pulaski, E J , Spicer, F W , and Johnson, M J (1948), *Ann Surg* , 46, 128
Schullinger, R N (1950), *Surg Clin North America*, 30, 495
Slattery, L R , Yannitelli, S A , and Hinton, J W (1950), *Arch Surg* , 60, 31
Tashiro, S , and Zinniger, M M (1946), *Arch Surg* , 53, 545
Theron, P H , and Wilson, W C (1949), *Lancet*, 1, 172
Wakeley, C , and Childs, P (1950), *Brit Med Journ* , 2, 1347
Wilkie, D P D (1931), *Brit Med Journ* , 1, 253
Wright, L T , Schreiber, H , Metzger, W I , and Parker, J W (1951), *Surg Gynec Obstet* , 92, 661

THE EOSINOPHILE CELLS OF THE BLOOD

A GENERAL REVIEW *

By R D T CAPE, B Sc , M B , Ch B , M R C P (Ed) †

SINCE the advent of the adrenocortical hormones interest has been considerably revitalised in the eosinophile cells of the blood It seems an opportune moment, therefore, to review the present state of our knowledge of these cells and to consider briefly the way in which ACTH and Cortisone are helping to clarify their function and their fate

ORIGIN AND MORPHOLOGY

While it is considered by some that the eosinophils may be developed in the tissues the general consensus of opinion is that they originate in the bone marrow (Samter, 1949) One notable exception is Duran-Jorda (1943) On the basis of extremely detailed histological studies he has advanced the hypothesis that the eosinophile polymorphs are the carriers of preformed red corpuscles from the gastric and intestinal mucosæ to hæmopoietic organs He suggests a cyclical process in which lymphocytes develop through the stage of Paneth cells in the bowel mucosæ to become eosinophils, and that the granules of eosinophils are preformed red cells which are finally extruded from the parent cell, which becomes once more a lymphocyte His studies are intriguing but so far remain completely unconfirmed, and one must therefore regard them with considerable reserve

The more orthodox view states that eosinophils develop from myeloblasts, passing through the intermediate stages of promyelocyte, myelocyte and metamyelocyte, in which the eosinophile granules make their appearance The eosinophile metamyelocyte becomes a staff and then a mature eosinophil and, in common with other members of the granular series, these more mature forms are the most numerous in the bone marrow Thus there is always a good potential supply of the cells immediately available in case of need

Eosinophile cells are described morphologically as having a diameter of 10-12 microns Their cytoplasm is filled by large, round or oval, pink-staining granules The cells are actively amœboid but move more slowly than neutrophils According to Osgood (1937) their duration of life is eight to twelve days compared with two to four days in the case of neutrophils The fate of the eosinophils is not specifically known, but polymorphs are reported as becoming senile and dying in the blood stream , some are excreted in the saliva while most are probably destroyed in the reticulo-endothelial system

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Control of Production and Release

The regulation of production and release of leucocytes from the bone marrow is under the influence of four factors These are, firstly, chemotaxis, secondly, a leucocytosis promoting factor, thirdly, the spleen and fourthly, the endocrine system

Whitby and Britton (1947) suggest that the stimulus for the production of leucocytes varies with the type of cell, but is in all cases largely chemotactic Thus an injection of nucleic acid or its salts will artificially stimulate a leucocytosis, a similar stimulus being provided under pathological conditions by infection with pyogenic cocci where the nuclein products of tissue destruction act as a definite stimulus In health the stimulus, they suggest, may be supplied by the nucleoprotein set free when senile polymorphs themselves break up and disintegrate Menkin (1938), Duthie and Chain (1939) and more recently Collumbine and Rydon (1946) have demonstrated that there is a substance, leucotaxine, which is produced at the site of inflammation and, acting by chemotaxis, draws leucocytes rapidly to the affected region Collumbine and Rydon (1946) showed that this substance, which may be a polypeptide containing tryptophane, was present in the fluid obtained from vesicles caused by mustard gas burns, in lung œdema fluid produced by phosgene and also, *in vitro*, by the action of pepsin and trypsin on blood fibrin and blood albumin One interesting observation was that the activity of this leucotaxine was destroyed by incubation with normal plasma or serum, but not incubation with serum from an animal in which a state of " shock " had been produced

Menkin (1943) also described a leucocytosis-promoting factor, a pseudo-globulin which, on intravenous injection, causes an increase in circulating leucocytes averaging 200 per cent , and hyperplasia of the bone marrow It has been obtained from turpentine effusions in dogs, and inflammatory serous effusions in man Normal serum yields none, but it can be demonstrated in the blood of animals suffering from an inflammatory process

The role of the spleen is complex The effect of splenectomy on the white cells appears to be well established There is the usual post-operative rise in polymorphs, but this rise is greater after splenectomy than after any other operation and usually persists for some weeks Lymphocytes and monocytes appear to be particularly increased After some weeks eosinophils are often particularly increased and may comprise 10 to 12 per cent of the differential count This eosinophilia may last for a year or more The effects of splenectomy on a large number of albino rats has been described by Palmer *et al* (1951) Following the operation the total leucocyte count increased approximately 100 per cent in seven days, and remained significantly elevated for seventy to ninety days, after which time there was a return to normal levels, the increase being in both neutrophile and mononuclear cells Removal of as much as 75 per cent of the spleen resulted in a leucocyte increase resembling in magnitude and duration only that of control operations When small portions of spleen were transplanted to other sites the response also resembled that which followed control operations If splenectomy was performed in one partner of parabiotic rats no rise occurred in the leucocyte count of either animal, but if both spleens were removed a persistent rise did take place When rats were made leucopenic by pteroylglutamic acid deficiency no rise occurred following splenectomy The authors claim that their results suggest a hormonal action of the spleen on the circulating leucocytes, which acts by controlling the rate of production and liberation of the cells from the bone marrow, although their results were not entirely conclusive There is general agreement that under certain conditions the spleen may destroy white cells but these authors' work suggests that this may not be its only role

The influence of endocrine factors on bone marrow is varied Thyroxine has been reported to stimulate it, particularly the myeloid series, but this is thought to be due only to its general stimulation of metabolism increasing the needs of the tissues for oxygen, to which the marrow responds Adrenalectomized rats are reported to develop a moderate hypochronic anæmia by Piliero *et al* (1950), who also point out that there is a rise in the percentages of the myeloid components including blast cells, eosinophils and young and mature neutrophilic elements Despite these marrow changes, however, no consistent trends were noted in the peripheral white cell picture with chronic adrenal insufficiency Quittner *et al* (1951) gave a massive single dose of Cortisone to male albino mice and a pronounced increase in myeloid erythroid ratio occurred in the marrow They thought that this change was due to an absolute increase of myeloid cells with a resultant increase in total cellularity The percentage of eosinophile cells in the marrow did not change They noted also a striking eosinopenia and lymphocytopenia in the blood and suggested a concept of blocking of the bone marrow as being responsible, or partly responsible, for this

Our knowledge of the functions of eosinophils until recently has been no more than speculative The most satisfactory way of considering it is to examine first the information available before the advent of the adreno-cortical hormones and then discuss what new light their advent has created This information can also be arbitrarily and similarly divided by considering first the various conditions which give rise to an eosinophilia, as on them the pre-corticoid knowledge was largely based, while the second information is intimately connected with eosinopenia

CAUSES OF EOSINOPHILIA

The normal level of eosinophils is 100 to 400 per cmm being approximately 1 to 4 per cent of the total white cells Differentials of 5 per cent or over are usually accepted as an eosinophilia The conditions which give rise to eosinophilia are numerous and varied, and there are many conditions which may, on occasions, give rise to an eosinophilia, but do not do so consistently These various conditions may be grouped as follows —

(1) Parasitic infestations these commonly and fairly consistently give rise to an eosinophilia which varies in degree but is usually around 20 per cent , examples being infestation with intestinal helminths of various kinds, cysticercosis, bilharzia, filariasis and others

(2) Allergic conditions this is a large group including asthma, food sensitivity, hay fever, urticaria and other allergic states The count may be as high as 10 to 60 per cent In addition anti-bacterial immunisation is believed always to be associated with some degree of eosinophilia, and it has been suggested that if the cells disappear from the blood between injections, treatment should be suspended until their return In the tuberculin reaction, and injections of foreign protein a tissue eosinophilia may be found at the site of injection, and in angioneurotic œdema the rise in eosinophile cells may be pronounced

(3) Skin diseases any infective or irritative condition of the skin may give rise to eosinophilia, for example, pemphigus, dermatitis herpetiformis, scabies, psoriasis, eczema, and prurigo It has been suggested that the element of a foreign protein may be present in such conditions owing to the breakdown of the epidermis and the absorption of the breakdown products

(4) Acute infections in the acute stage of scarlet fever and rheumatic fever, especially associated with chorea, an eosinophilia of up to 10 per cent has been reported There is, however, an equally strong, if not stronger view, that this occurs only in the convalescent stage Friedman and Holtz (1935) have suggested that the progress and prognosis of rheumatic fever might be assessed by repeated eosinophile counts, a lack of eosinophils being noted in the acute phases, with or without an active cardiac condition, while a post-infection eosinophilia may develop during recovery A prolonged period of eosinophile lack indicated intense severity of the disease, while continuous eosinophilia indicated convalescence This response is characteristic of the behaviour of the eosinophile cells in any uncomplicated acute infection

(5) Drugs pilocarpine, phosphorus, camphor, copper sulphate, mercury, arsenic, acetanilide, sodium salicylate, and digitalis are all reputed to cause eosinophilia on occasion Nirvanol, a barbituric acid derivative formerly used in the treatment of chorea, may cause a drug eruption with fever and pronounced eosinophilia

(6) Finally, the other conditions which may show eosinophilia at times, but do not do so constantly, include periarteritis nodosa, a case of which Stong reported in 1928 with an eosinophilia of 79 per cent , Hodgkin's disease in which there are frequently quite a number of

eosinophile cells in the affected glands and occasionally in the peripheral blood, malignant disease, ulcerative colitis, some cases of Addison's disease and X-ray or radium treatment

Eosinophils may be found also in large numbers in hæmorrhagic pleural fluid, intestinal blood and mucous from cases of bacillary dysentery, the sputum of asthmatics, and nasal secretions of cases of vasomotor rhinitis

There are four conditions, all of them rare, in which there is a particularly marked eosinophilia These are (1) eosinophilic leukæmia, (2) eosinophilic granuloma of bone, (3) Loeffler's Syndrome and (4) tropical eosinophilia

In eosinophilic leukemia, which is almost invariably associated with a palpable spleen, leucocytes are commonly from 20,000 to 80,000 and may be as high as 250,000 The predominant cell is a mature eosinophil Whitby and Hynes (1936) report that the cells are unusually motile The granules vary in size and are usually much larger than in normal eosinophils Often they do not fill the cell, and in a Leishman stained film there may be large unstained spaces giving the appearance of vacuoles (Whitby and Britton, 1947) Their phagocytic power has been tested and found to be one-third as active against staphylococcus aureus as polymorphs Eosinophile myelocytes are present only in small numbers, the average being from 0 5 to 2 per cent with a maximum of 5 per cent Other cells are present in normal absolute numbers The disease runs a chronic course and the average expectation of life is about six years A few very acute cases have been reported where death has occurred in as short a period as three days (Stephens, 1935 , Hay and Evans, 1929) Splenectomy does no good Drennan and Biggart (1930) succeeded in producing a temporary drop in the eosinophile count from 23,000 to 7900 by three injections of a splenic extract but the count later rose to 49,000 prior to death

Eosinophilic granuloma of bone is a condition affecting mainly children and adolescents The lesions may take the form of single or multiple foci in bones, each consisting of sheets of large histiocytic cells among which are more or less conspicuous numbers of eosinophile cells, particularly eosinophile leucocytes There are also areas of necrosis present around which actively phagocytic multinuclear giant cells are present Jaffe and Lichtenstein in 1944 suggested that the lesions may heal by resolution They point out that in multiple cases most of the lesions are silent and suggest that many " single focus " cases may never be seen at all The X-ray appearances are not distinctive and may be confused with those of primary cancer In the multiple cases the appearances on X-ray resemble those found in multiple myeloma, Ewing's tumour or secondary carcinomatous metastases The appearances in the skull may simulate Hand Schuller-Christian Disease These authors share the view of others (Gross and Jacox, 1942 , Mallory, 1942) that this condition, Hand Schuller-Christian Disease and Letterer Siwe Disease constitute different clinical expressions of the same basic disorder, which seems to have a predilection for the hæmopoietic system Its lesions apparently represent a peculiar inflammatory reaction to some as yet unknown infectious agent and are characterised cytologically at their outset by the presence in them of large numbers of histiocytes

Loeffler's Syndrome and tropical eosinophilia have several features in common and can be considered together The main characteristics of each are tabulated in Table I, which is based largely on data given by Apley and Grant (1944) and Weingarten (1943) The view of the former authors is that there are insufficient grounds for dividing the two conditions They quote cases between the two extremes, such as a typical example of tropical eosinophilia in an English airman in Cairo (Parsons-Smith, 1944) and cases of Loeffler's Syndrome outside Europe with a previous history of bronchitis related to humidity (Freund and Samuelson, 1940) Their conclusion is that the association of two such findings as pulmonary infiltrations and eosinophilia is so striking that its occurrence in two completely unrelated diseases appears improbable That there is a definite difference, however, in the response to ACTH therapy has been shown recently by Herbert, DeReis and Rose (1950), who were able to get a dramatic reduction of the eosinophilia in a case of Loeffler's syndrome, but obtained only a rather poor response with a case of tropical eosinophilia There are no records of cases of Loeffler's syndrome treated with arsenic

TABLE I

Clinical Features of Löeffler's Syndrome and Tropical Eosinophilia

	Loeffler s Syndrome	Tropical Eosinophilia
RACE	European	All races
CLIMATE	Dry	Tropical and humid, *e g* Indian coastal regions
ONSET	Mild—Few symptoms	Insidious with later acute episode
COURSE	Mild—Little systemic disturbance, transient	Chronic—Night cough and asthma—Loss of weight
DEGREE OF EOSINOPHILIA	Variable and transient (up to 66 per cent)	Variable and persistent (up to 89 per cent)
SPLENOMEGALY	No	Yes—in acute episode
X RAY	Shadowing of the lungs, variable in type always resolving quickly	Disseminate mottling of both lungs in second week of illness After acute phase changes of chronic bronchitis
PROGNOSIS	Speedy spontaneous recovery	Chronic disease unless treated with arsenic

CAUSES OF EOSINOPENIA

For some time it has been realised that a variety of conditions give rise to eosinopenia, such as hæmorrhage, cold, hæmolysis, poisons, operative procedures and a wide variety of infections Selye (1949) in his concept of the general Adaptation syndrome has included this eosinopenic effect as part of the " Alarm Reaction " Hills, Forsham and Finch (1948) have demonstrated that ACTH and Compound F produced a decrease in the number of circulating eosinophils and have shown that the conditions which call forth this effect are all stress stimuli Thorn and his associates (1948) have shown that the presence of an active suprarenal cortex is necessary for the eosinopenic effect to occur

The mechanism by which the release of the corticoid substances is obtained is rather a complex one Hume (1949) has carried out some interesting experiments on dogs, and, based on their results, he has suggested that three factors are necessary for the mechanism to take place These are firstly, an intact hypothalamus, secondly, transmission of a hormonal stimulus to the anterior pituitary by the hypothalamus, and thirdly, in the case of trauma, an intact nervous connection between the injured area and brain The mechanism which Hume envisages is shown diagramatically in Fig 1, which is based on the results of his experiments

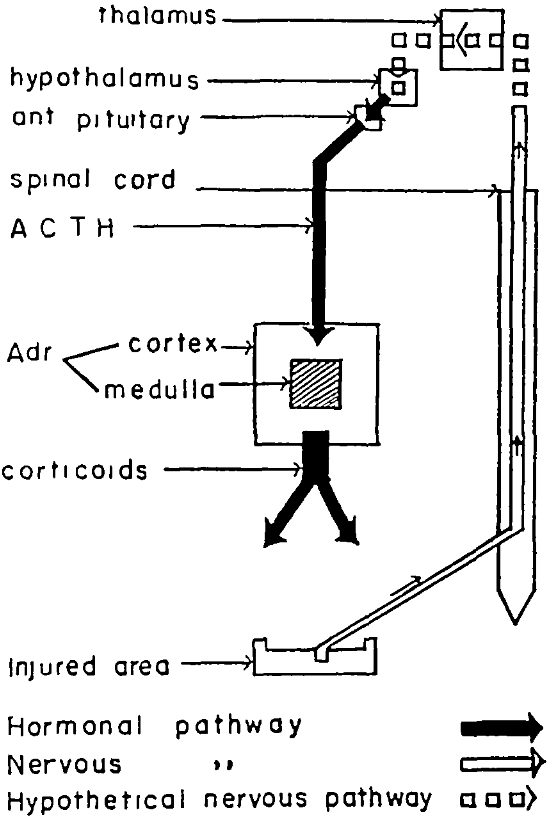

FIG 1 —Pathway of stimulus causing release of corticoids and eosinopenia (after Hume 1949)

Among the functions of the hypothalamus is the control of the diurnal rhythm of body temperature and sleep Rud (1947) in a very elaborate statistical analysis of the behaviour of normal eosinophils showed that there were significant and constant diurnal variations of eosinophile levels with a drop in the forenoon and a rise in the afternoon and evening According to Godlowski (1948) sleep itself tends to speed up the recovery of normal levels of eosinophils after an eosinopenia produced in his cases by insulin shock and the consequent release of adrenalin He and others (Eppinger and Hess, 1909) have suggested that parasympathetic stimulation, for example pilocarpine, stimulates an eosinophilia, while sympathetic stimulation produces an eosinopenia Autonomic control is vested in the hypothalamus Thus we see that these observations tend to confirm indirectly the concept of Hume regarding the control of the eosinopenic mechanism

FATE OF EOSINOPHILS IN EOSINOPENIA

What is the fate of the eosinophils when they disappear from the peripheral blood after ACTH administration? One of three things must occur, lysis of the cells, sequestration of the cells out of the blood stream into the tissues of the body, or "blocking" of the bone marrow Godlowski (1951) has suggested that the first process occurs He has demonstrated, in a limited series, the fact that patients or animals whose clotting mechanism has been virtually abolished by heparin do not respond to ACTH by an eosinopenia He shows also that heparin, *per se*, will cause an eosinophilia He concludes that "the explanation of these phenomena lie in the two apparently independent actions of heparin and eosinopenic hormones Heparin mobilises the tissue eosinophils arrested in the lymphoid tissue during the interaction between antigen, carried by eosinophils, and specific antibodies, discharged from lymphocytes, shifting them into the circulation Eosinopenic hormones, on the other hand, exert a direct eosinolytic action causing their disintegration in the circulating blood" Recent studies in the Metabolic Unit have shown that such an effect does not occur *in vitro* (Cape, Thomas and Palmer, 1952), an observation confirmed by other authors (Thorn, Forsham *et al*, 1951)

The question of possible sites for sequestration of eosinophils is a difficult one The reticuloendothelial system and particularly the spleen have been suggested, but there is evidence, in animals at least, that splenectomy does not interfere with the normal eosinopenic response to epinephrine (Lucia, Leonard and Falconer, 1937) The reticulo-endothelial system, however, is a very widespread and rather unapproachable one Other sites where the eosinophils may hide out have been suggested, such as the intestine, lungs, and salivary glands

Regarding the third possible mechanism, Durgin and Meyer (1951) have recently examined the bone marrow of mice who were given lipo-adrenal extract There was a marked increase in the younger stages of eosinophile cells indicating an active production of new cells by the bone marrow They point out that cells which are proliferating rapidly do not undergo much cellular differentiation and that consequently, in bone marrow thus stimulated, differentiation of cells into mature forms and the release of mature cells into the circulating blood would not occur so rapidly as in bone marrow which did not show increased activity They add that it is generally accepted that the granular leucocytes, as well as the lymphocytes, migrate from the blood vessels into the tissues and digestive tracts This, they suggest, may occur more rapidly under the influence of the adrenocortical hormones, or the hormones may have some effect on the eosinophils themselves

COMMENT ON FUNCTIONS OF EOSINOPHILS

To conclude, I would like to draw attention to one particular aspect of this problem In acute infections the behaviour of the granular series of white blood cells in the majority of cases is typified in the acute phase by a polymorphic leucocytosis and an absence of eosinophils As the process resolves and convalescence begins we find that the polymorphs return to normal, or even below normal, while the eosinophils reappear and often go on to a higher level than normal Fig 2 illustrates very hypothetically the type of response envisaged It seems to me that there is probably a correlation between these effects It is reasonable to suppose that emanating from the same source and by the same mechanism the control of the granular series of leucocytes is unified Any stress, or ACTH, I believe, produces this stereotyped response and, in the light of our present knowledge, it appears that it is mediated through the activity of the supra-renal cortex

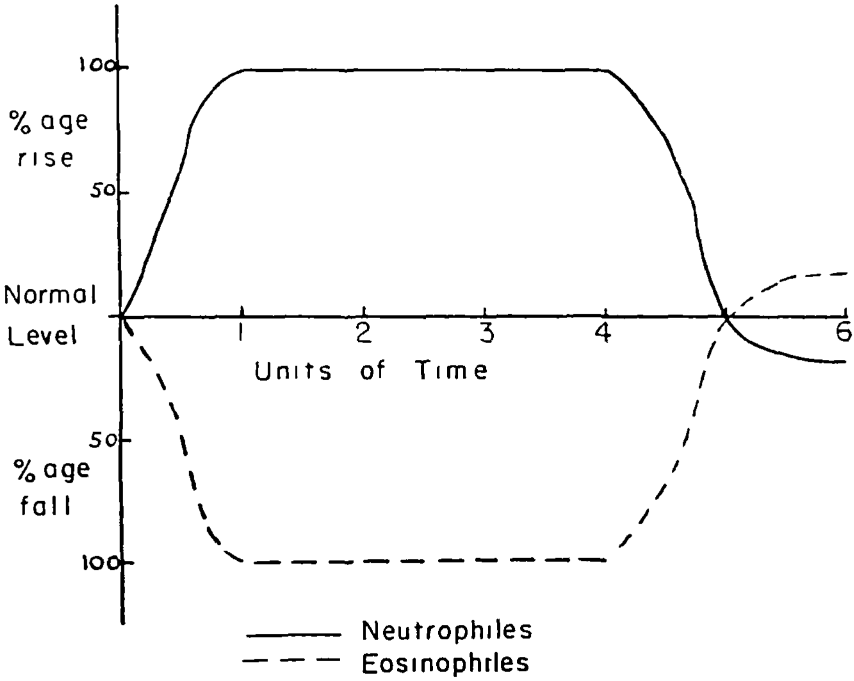

FIG 2 —Diagrammatic representation of response of granular series of white cells to acute stress (see text)

During the recovery period from an acute infection most patients have developed at least a temporary immunity to the organism responsible for their infection Most of the conditions with prominent eosinophilia are considered to have an " allergic " basis It is accepted that the main function of the white cells of the blood is a defensive one I would suggest that the eosinophil is the second line of defence, that its function is intimately associated with the development of immunity, if I may use that word in a broad sense, and that the eosinopenia following stress is the result of a stimulus to the bone marrow which causes immediate release of polymorphs, while at the same time, and perhaps to facilitate this, withholding release of the less urgently needed eosinophils Then, during a period of three to four hours, eosinophils in the blood before the stimulus may pass out into the tissues or digestive tract, as suggested by Durgin and Meyer (1951)

Conclusions cannot be based on speculations, however, attractive There is a well-established link between allergic processes and eosinophilia, and Godlowski (1948*b*) has shown that the eosinophils may act as " anaphylactogenic carriers " A definite quantitative relation between the two conditions, however, is still lacking in spite of attempts to reveal it (Campbell, Drennan and Rettie, 1935) On the other hand Cortisone and ACTH have been shown to combat many allergic manifestations and appear to have an effect in immune mechanisms Again, however, the nature of this effect remains tantalisingly obscure Undoubtedly the future will clarify relationships between these four factors, eosinophilia and allergy, on the one hand, and eosinopenia and the adrenocortical hormones on the other, and in so doing perhaps more complete knowledge will be obtained of the functions of the eosinophil

SUMMARY

1 The present view is that the eosinophils of the blood are formed in bone marrow and survive for between eight and twelve days in the blood

2 The stimulus to formation and release of the cells from bone marrow is under the control of four possible factors, chemotaxis, a leucocytosis-promoting factor, the spleen and various hormones

3 The causes of eosinophilia are outlined The main groups of conditions considered are (*a*) Parasitic infestations, (*b*) Allergic conditions, (*c*) Skin diseases, (*d*) Acute infections, (*e*) Drugs, (*f*) Eosinophilic leukemia, eosinophilic granuloma of bone, Loeffler's Syndrome and Tropical eosinophilia

4 The causes of eosinopenia are all essentially stress stimuli The nature of the mechanism producing this and the nervous and humoral pathways involved are considered

5 The fate of the eosinophils during eosinopenia is discussed, under three possibilities (*a*) Destruction of the cells in the blood stream, (*b*) Sequestration of the cells out of the blood stream, (*c*) " Blocking " of the bone marrow

6 Comment is made on the possible nature of the functions of eosinophils, and the relationship of allergy and eosinophilia on the one hand and eosinopenia and the adrenocortical hormones on the other, is noted

BIBLIOGRAPHY

APLEY, J , and GRANT, G H (1944), *Lancet*, 2, 308-309

BALDRIDGE, G D , *et al* (1951) *Amer Med Assoc Arch Path* 51, 593

CAMPBELL, A C P , DRENNAN, A M , and RETTIE, T (1935), *Journ Path Bact* , 40, 537

CAPE, R D T , THOMAS, J W , and PALMER, R A (1952), *Can Med Assoc Journ* , 66, 441

COLLUMBINE, H , and RYDON, H N (1946), *Brit Journ Exper Path* , 27, 33-46

DRENNAN, A M , and BIGGART, J H (1930), *Journ Path Bact* , 33, 995

DURAN-JORDA, F (1943*a*), *Lancet*, 1, 513-514

DURAN-JORDA, F (1943*b*), *Lancet*, 2, 186-188

DURGIN, M I , and MEYER, R K (1951), *Endocrinology*, 48, 518

DUTHIE, E S , and CHAIN, E (1939), *Brit Journ Exper Path* , 20, 417-429

EPPINGER, H , and HESS, L (1909), *Ztschy f Klin Med* , 67, 345 Quoted by BEST, W R , and SAMTER, M (1951), *Blood*, 6, 61-73 , and GODLOWSKI, Z Z (1948), *Brit Med Journ* , 1, 46-48

FRUEND, R , and SAMUELSON, S (1940), *Arch Int Med* , 66, 1215-1220

FRIEDMAN, G , and HOLT, E (1935), *Journ Lab Clin Med* , 21, 225

GODLOWSKI, Z Z (1948*a*), *Brit Med Journ* , 1, 46-48

GODLOWSKI, Z Z (1948*b*), *Brit Journ Exper Path* , 29, 511

GODLOWSKI, Z Z (1951*c*), *Brit Med Journ* , 1, 854

GROSS, P , and JACOX, H W (1942), *Amer Journ Med Sci* , 203, 673-687

HAY, J , and EVANS, W H (1929), *Quart Journ Med* , 22, 167

HERBERT, P , DE VRIES, J A , and ROSE, B (1950), *Journ Allergy*, 21, 12-24

HILLS, A G , FORSHAM, P H , and FINCH, C A (1948), *Blood*, 3, 755-768

HUME, D M (1949), *Journ Clin Invest* , 28, 790

JAFFE, H L , and LICHTENSTEIN, L (1944), *Arch Path* , 37, 99-118

LUCIA, S P , LEONARD, M E , and FALCONER, E H (1937), *Amer Journ Med Sci* , 194, 35

MALLORY, T B (1942), *New Eng Journ Med* , 227, 955

MENKIN, V (1938*a*), *Physiological Review*, 18, 366

MENKIN, V (1943*b*), *Amer Journ Path* , 19, 1021

OSGOOD, E E (1937), *Journ Amer Med Assoc* , 109, 933

PALMER, J G , *et al* (1951), *Blood*, 6, 3-15

PARSONS-SMITH, B G (1944), *Lancet*, 1, 433-434

PILIERO, S J , LANDAN, D , and GORDON, A S (1950), *Science*, 112, 559

QUITTNER, H , *et al* (1951), *Blood*, 6, 513-521

RUD, F (1947), *Acta psychiat et neural* , Supp 40, 1-443 Quoted by LEADER (1950), *Lancet*, 1, 1042

SAMTER, M (1949), *Blood*, 4, 217

SELYE, HANS (1949), *Textbook of Endocrinology* Acta Endocrinologica, Inc , Montreal, Canada Second edition

STEPHENS, D J (1935), *Amer Journ Med Sci* , 189, 387

STRONG, G F (1928), *Can Med Assoc Journ* , 19, 534

THORN, G W , FORSHAM, P H , PRUNTY, F T , and HILLS, A G (1948), *Journ Amer Med Assoc* , 137, 1005

THORN, G W , FORSHAM, P H *et al* (1950), *New Eng Journ Med* , 242, 783

WEINGARTEN, R J (1943), *Lancet*, 1, 103-105

WHITBY, Sir L E H , and BRITTON, C J C (1947), *Disorders of the Blood* London J & A Churchill

WHITBY, Sir L E H , and HYNES, M H (1936), *Journ Path Bact* , 43, 91

BRONCHOSCOPY

MEDICAL DIAGNOSIS AND TREATMENT

By I MALCOLM FARQUHARSON, F R C S (Ed)

IT will be my endeavour in this paper to review the progress that has taken place in bronchology and to indicate its present status in diagnosis and treatment of broncho-pulmonary disease

In its early beginnings bronchoscopy was associated only with the removal of foreign bodies in the air passages Now bronchology is a recognised specialty and bronchoscopy a proved method in the diagnosis and treatment of bronchial disease

In addition to its diagnostic and therapeutic value, bronchology has contributed considerably to our knowledge of the physiology of the tracheo-bronchial tree It has explained the value of peroral drainage, by ciliary wafting, tussive squeeze and bechic blast in expelling partially obstructive material before it accumulates

Chevalier Jackson in his monumental work on this subject has explained the mechanism of obstructive emphysema and atelectasis and the interpretation of their physical signs

In dealing with bronchial obstruction bronchoscopy has made possible many recent advances of modern anæsthesia, and the bronchoscope is now an established part of an anæsthetist's equipment

In the management of intrathoracic disease the bronchoscopist has become a member of a diagnostic team, comprising the Physician and the Radiologist By his ability to view the interior of the lung and to remove specimens of tissue and uncontaminated secretion, he can render invaluable aid in diagnosis

In order to obtain the greatest assistance from such an examination the bronchoscopist must be familiar with the intricate anatomy of the bronchial tree He must think not only of lobar bronchi and lobes but rather of segmental bronchi and broncho-pulmonary segments, so that, on viewing a bronchial orifice, he will know to what portion of lung each orifice leads, its relative size, importance and relations

In the same way, on viewing an X-ray film he should be able to tell not only in which lobe, but also in which segment, a lesion or foreign body is lying, and he may then proceed to locate the particular bronchus leading to it

By this method alone can our bronchoscopic reports be of greatest value to our medical and surgical colleagues

The majority of cases are referred to us from the medical wards of the hospital, and of these cases the greatest number are those in which the radiologist has reported the presence of a doubtful shadow, suggestive of a neoplasm

A Honyman Gillespie Lecture given on 16th November 1950

As this type of case figures so prominently in our clinic I wish to deal first with the diagnostic problems of bronchogenic carcinoma

There is general unanimity among clinicians that the only successful treatment is operative

Adrian Lambert reviewing the cases treated at the Bellevue Hospital, New York, between 1939-46—349 cases—states that 20 per cent of the cases admitted with carcinoma of the bronchus were considered suitable for operation Seventy were explored and only 25 had a tumour which was removable , of these 7 died in hospital

Rienhoff of Johns Hopkins describes a similar experience—327 cases of which 215 were inoperable and 112 cases operable—39 per cent survived operation

Brock in this country has a similar tale to tell One and all explain these gloomy figures as due entirely to the fact that the cases were not diagnosed early enough

In reviewing case histories of many of these patients found to be inoperable, one is struck by the fact that the correct diagnosis could have been made at a much earlier date if the significance of certain vital signs and symptoms had been appreciated and if the need for X-ray and bronchoscopy had been realised

The signs and symptoms of greatest significance are —

(1) Persistent cough, with or without blood-stained sputum, seen in 50 per cent of the cases Brock suggests in patients between forty and sixty it is almost diagnostic
(2) Symptoms of respiratory infection—slowly resolving and recurring pneumonia
(3) Henkin Triad—fever, leucocytosis, anæmia
(4) Pain in the chest—late
(5) Wheezing

These, however, are protean symptoms

Norris from the Chevalier Jackson Bronchoscopic Clinic has suggested that the early manifestations of a bronchial carcinoma depends to a large extent on its point of origin, so that an arbitrary classification based on location is of more practical value for clinical study

Separate consideration might be given to those tumours which arise in the main or lobar bronchus, those which arise in the segmental and those arising peripherally

It is generally held that over 50 per cent of carcinoma arise in a main or lobar bronchus, a much smaller number in one of the segmental bronchi and some 25 per cent arise peripherally

SYMPTOMS OF A CARCINOMA OF THE MAIN OR LOBAR BRONCHUS

The earliest symptom is bronchial irritation—chronic unproductive cough—this is followed by symptoms dependent upon increasing bronchial obstruction which interferes with the air exchange and drainage In its lesser degrees giving rise to a wheeze localisable to one or other side—the " asthmatoid wheeze " described by Chevalier Jackson

When the obstruction is more marked, interference with the normal bronchial drainage gives rise to secondary infection resembling one of the common lower respiratory infections—bronchitis or pneumonia

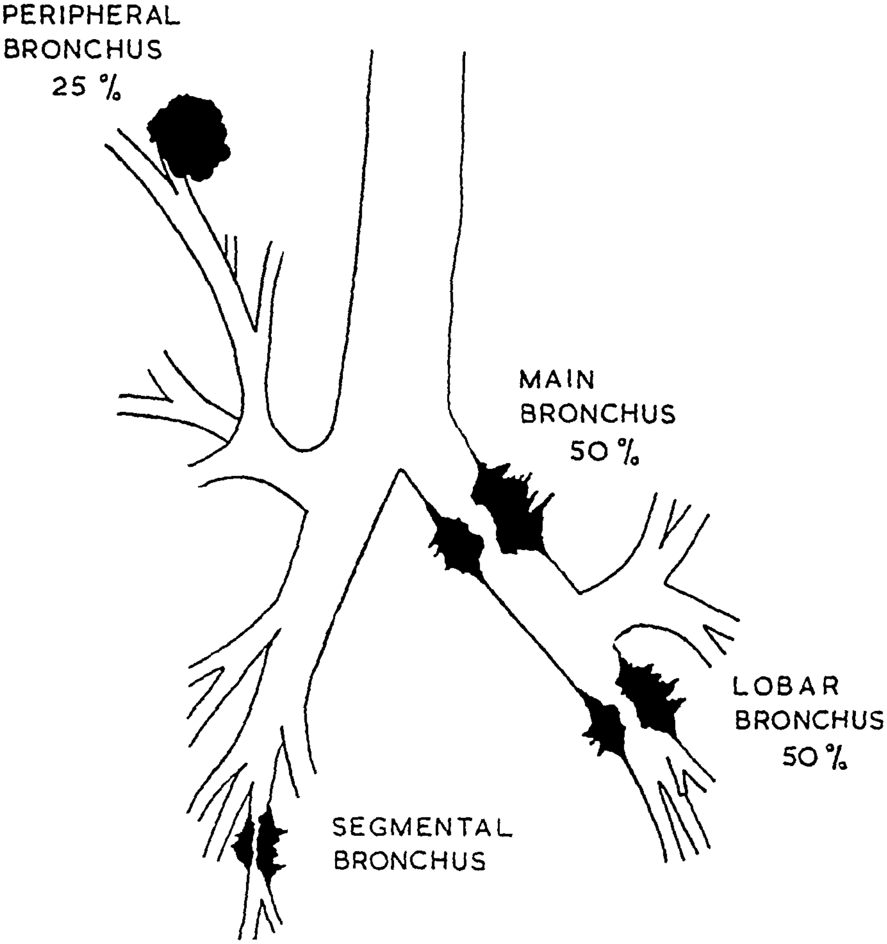

FIG I —*Bronchogenic carcinoma* —Arbitrary classification Based on location The early clinical and X ray findings depending on the position of the tumour (Adapted from Charles M Norris, M D , F C C P , *Diseases of the Chest*)

Hæmoptysis occurs early when one of the larger bronchi is involved At the outset, therefore, there may be no abnormal physical signs or X-ray findings Their appearance proclaims the presence of some degree of bronchial obstruction The existence of a tumour, therefore, is suspected because of the effect it has upon the air exchange and bronchial drainage

The earliest physical signs will be smaller respiratory excursion

It will be realised that the only way of making a positive diagnosis of bronchogenic carcinoma prior to operation is by microscopic examination of a piece of the tumour

In reviewing the literature it is found that a diagnosis was made by biopsy in 60 to 80 per cent of cases

Louis Clerf at the Jefferson Hospital from 1930-45 recorded a positive biopsy rate of 65 per cent in 336 cases Holinger 70 per cent in 175 cases Overholt 62 per cent

The figures at the Royal Infirmary, Edinburgh, and Bangour Hospital, show a positive biopsy rate of 60 per cent

TABLE I

Radiotherapy Department, Royal Infirmary, Edinburgh

Cancer in Lung 1935-48

Showing the Number of Cases of Carcinoma of the Lung 1935-48 *It is Interesting to Note there is a Considerable Increase in Numbers in More Recent Years*

Number bronchoscoped and histologically proven bronchoscopically	242
Number otherwise proven, *i e* by post mortem or biopsy of gland or metatastic deposit	408
Number not proven	623
Total number	1273

Cancer in Lung	1935	1936	1937	1938	1939	1940	1941	1942	1943	1944	1945	1946	1947	1948	Total
Bronchoscoped and histological +	2	3	4	8	7	11	9	20	20	30	24	23	23	58	242
Gland or metastases + post mortem +	12	6	25	15	18	17	14	25	12	33	35	48	77	71	408
Not histologically proven	13	18	21	27	36	41	37	42	59	69	62	69	62	67	623
Total	27	27	50	50	61	69	60	87	91	132	121	140	162	196	1273

At first sight these figures may appear encouraging until they are offset by the number of cases successfully operated upon—few surgeons would claim higher than 10 to 15 per cent of the total number

It has appeared that the higher the percentage of positive bronchoscopic biopsies, the higher the percentage of inoperable cases

From this survey it is evident that in order to treat this disease successfully an earlier diagnosis must be made, before the large bronchi become obstructed, and a search made for the lesions outside the visual field of the bronchoscope—in the peripheral bronchi and upper lobe

In an endeavour to overcome these technical difficulties use has been made of the retrograde telescopic lens system for the upper lobe lesions, but this did not fulfil the hopes placed in it Pneumothorax in the upper lobe lesions was employed but did little to improve the radiological visualisation of the tumours

Aspiration biopsy has been employed to gain this end successfully but has been condemned by the thoracic surgeon because of the danger of cancer implantations down the track of the needle

In this country, Barnett, Dudgeon and Gower examined the sputum for malignant cells and claimed a high percentage of accurate results These claims, however, have not been universally confirmed

Since there is a constant exfoliation of cells from the free surface of a tumour, direct examination of the bronchial secretion would appear to give more hopeful results

This method was employed by Herbut and Clerf who, seeing the excellent results obtained in carcinoma of the uterus by the Papanicolaou technique, resolved to adapt it for use in the diagnosis of carcinoma of the bronchus

A review of their results showed that they obtained a positive cytological diagnosis in 22 out of 30 cases—73 per cent—of proved carcinoma In this same group the histological diagnosis of carcinoma based on bronchoscopic biopsy was 36 6 per cent

Since the introduction of the cytological study of bronchial secretion in 1946 certain changes in technique have been made

Now in all cases an X-ray is taken to aid the localisation of the lesions to a lobar segment, lobe or lung, and then a routine bronchoscopy is performed for diagnostic purposes, secretions from the trachea and larger bronchi are discarded as marked dilution and disintegration of cells occurs Secretions are collected in a special collector from the bronchial divisions under suspicion and are sent for pathological examination

The introduction of a few c c of normal saline into the bronchus under examination, and its reaspiration after a few minutes, aids in the collection of material

In examining the upper lobe better results are obtained by placing the patient on the affected side, after the bronchoscope has been introduced, and aspirating as before

Louis Clerf and Herbut in 1947 carried out a follow-up study to determine the comparative value of cytological diagnosis and other accepted methods

The total number of observed cases was 180, all known cases of carcinoma based upon bronchoscopic biopsy, exploratory thoracotomy, post mortem and cytological study

All cases diagnosed by cytology were corroborated by one of the previously mentioned methods

It was further noted that a proportionately larger number of bronchoscopically negative, cytologically positive, cases were amenable to surgical removal, than bronchoscopically positive cases alone This, of course, was due to the earlier diagnosis made possible by this method, and to the fact that the situation of the growth was segmental, rather than lobar, in origin

I should like to mention here, while discussing the cytology of bronchial secretions, the further use of this technique by Clerf and Herbut as an aid to the diagnosis of early pulmonary tuberculosis

These workers, while studying bronchial secretions for cancer cells, were puzzled by the presence of, in some cases, rounded clusters of ciliated epithelial cells, single ballooned and vacuolated ciliated epithelial cells, and giant cells of the Langhans type

All cases save one, in which these cells were found, gave a subsequent positive culture of tubercle bacilli some months later

The authors explain the phenomenon by suggesting that there must be a tuberculous ulcer of the epithelium of the bronchus at the level where the epithelium becomes ciliated In the process of ulceration the cells break off in clumps, and, since they are spontaneously sloughing, their borders are rounded

This method is particularly helpful in differentiating pulmonary tuberculosis from carcinoma in atypical lesions

As yet I have no personal experience of this further application of the Papanicolaou technique

BRONCHIAL OBSTRUCTION

Bronchial obstruction may be defined as any morbid diminution of the lumen of the bronchus

Bronchial obstruction enters into every medical and surgical problem of pulmonary disease, and a knowledge of the subject is fundamental to an understanding of these diseases

It may be said that no one goes through life without encountering bronchial obstruction in one form or another

Our knowledge of this subject is due almost entirely to the pioneer work of Chevalier Jackson to whom we owe so much for an understanding of this vital subject

He has explained the physiology of the bronchial mechanism and the mechanics of bronchial obstruction His work, more than any other, has been responsible for the saving of countless lives and the making possible of so many of the advances of surgery and anæsthesia

PHYSIOLOGICAL BASIS OF BRONCHIAL OBSTRUCTION

The cough reflex has been aptly termed the " Watch dog of the lung " Upon its vigilance rests the safety of the lower air passages, being ever ready to extrude any exogenous or endogenous intruders from the lumen of the bronchus

The normal mechanism of pulmonary drainage is dependent upon three main factors

(1) The ciliary wafting
(2) The tussive squeeze
(3) Bechic blast

These three forming what has been called the mechanism of normal peroral pulmonary drainage

When the function of any of these three is interfered with some degree of bronchial obstruction will ensue

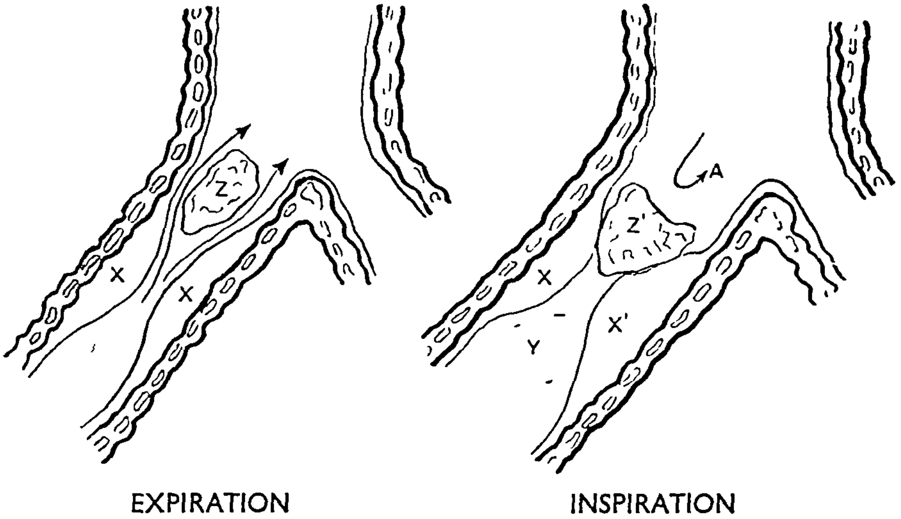

FIG 2—*Mechanism of obstructive atelectasis* produced by a mass of secretion (Z) acting like a check valve in a pump It rests on a ridge of swollen bronchial mucous membrane at the opening of a bronchus (X) At each expiration it is lifted by the expiratory current, allowing air to escape At the beginning of inspiration the suction pulls the mass down (Z′) tightly as on a valve seat so no air can enter (A) The final result of this will be atelectasis A mass of secretion (Y) below the inflammatory narrowing (X′) would cause a pumping in of air and so emphysema (Adapted from Jackson and Jackson, *Diseases of the Nose, Throat and Ear*)

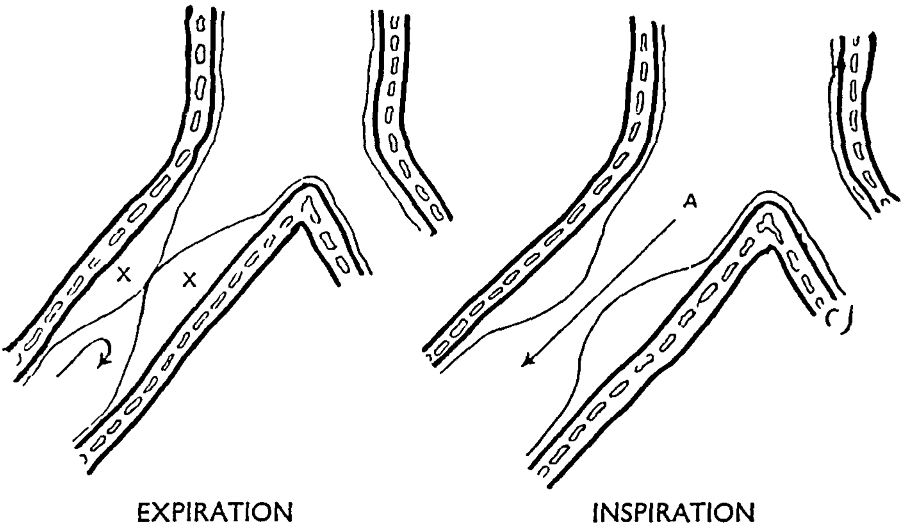

FIG 3—*Expansile check valve*—The swollen mucous membrane (X) comes in contact at the commencement of the start of the expiratory phase, the bronchial diameter is sufficient to make an opening for the admission of air (A) At the beginning of the following expiratory phase the diminution of the bronchial diameter closes the narrow lumen, trapping air below the obstruction Obstructive emphysema will result in that tributary area (Adapted from Jackson and Jackson, *Diseases of the Nose, Throat and Ear*)

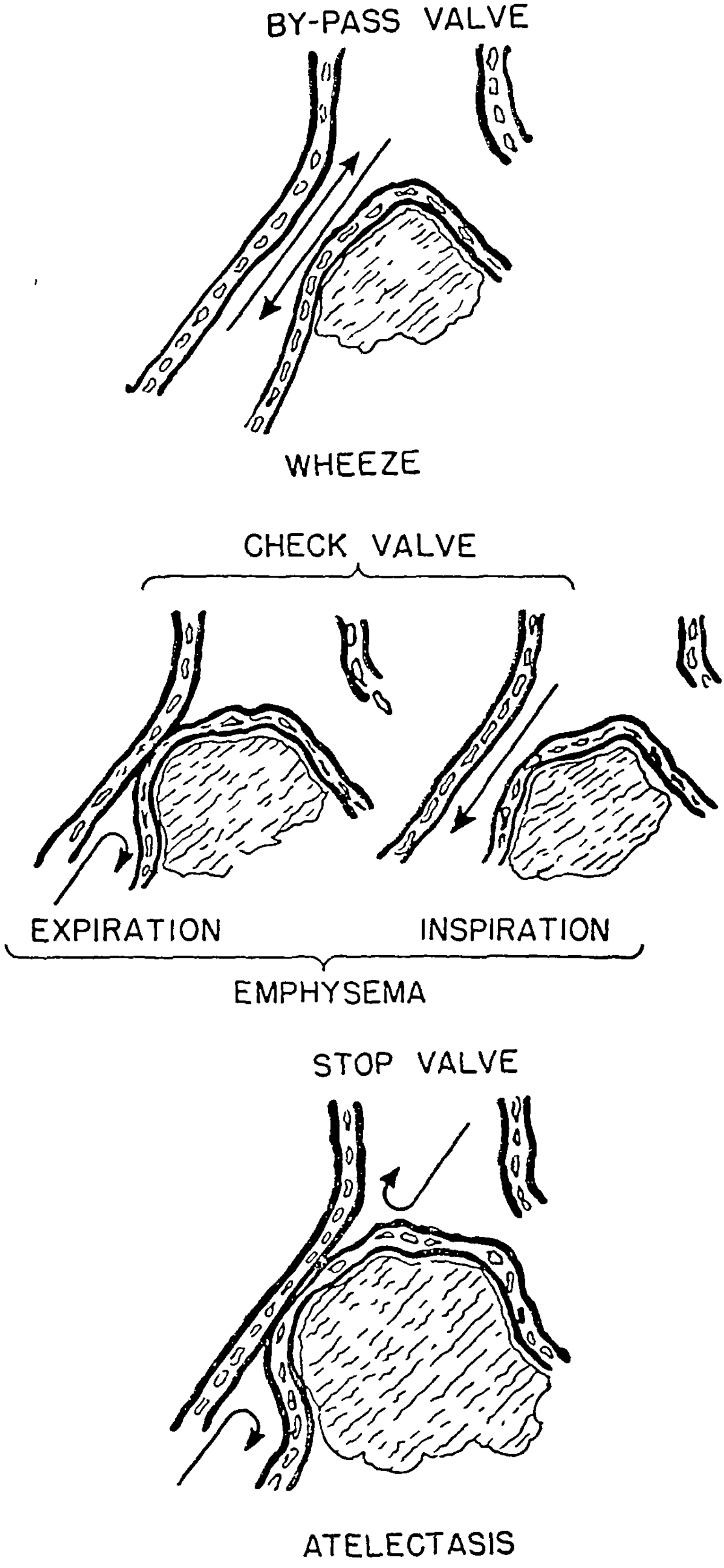

FIG 4 —Showing the method whereby a peri bronchial lesion, tuberculous or malignant gland, can produce three different types of bronchial obstruction with their own physical signs (Adapted from Jackson and Jackson, *Diseases of the Nose, Throat and Ear*)

The first factor, of course, must be a diminution of the bronchial lumen

The three elements of peroral drainage may be upset by many factors, for example —

The ciliary wafting may be thrown out of action either by a clogging of the cilia by mucosal swelling or by the adhesive and cohesive nature of the bronchial secretions

The bechic blast, being the principal vehicle for removing pathological material, is dependent for its action on the pressure of air below it, so that in the event of bronchial obstruction its action is limited In such a case it is dependent upon the tussive squeeze for supplying it with secretion for expulsion

An auxiliary agent is the movement of the tracheobronchial tree constituting a rhythmic enlargement and elongation of the lumen and a diminution and shortening of the lumen—this alternating eighteen or more times per minute

THE MECHANICS OF BRONCHIAL OBSTRUCTION

The bronchoscope may be said to have revolutionised one's conception of bronchial obstruction

Chevalier Jackson has shown how the problem is related to the science of mechanics, involving the action of forces upon bodies both solid, liquid and gaseous

Bronchoscopic examination revealed the fact that obstruction in the living is valvular in action

Valvular obstruction of the bronchus is dependent upon the normal movements within the bronchus

The different types of valvular action that may occur have been described as —

(1) Stop-valve—arresting all flow of air
(2) By-pass valve—allowing a limited flow of air in both directions
(3) One way valve—allowing a flow in one direction only

The one way or check valve will permit the entrance of air into a lobe but prevent exit of air from it

This will give rise to an emphysema of the lung below

The ball-like action of these valves may be produced by a mass of secretion falling back on an annular stricture formed by œdematous mucous membrane or a tumour mass in the bronchus

In the case of a foreign body lying in a bronchus, at first air may be seen to pass down between it and the bronchial wall by a mechanism of enlargement of its lumen on inspiration, while on expiration no upward passage of air occurs This gives rise, initially, to an emphysema of the lung below the foreign body, later reactionary swelling of the mucosa around the foreign body occurs and no air passes in either direction Emphysema is thus followed by atelectasis

Bronchial obstruction is commonest at the extremes of life, occurring in the new born babe as an inhalation of amniotic fluid and in the aged as hypostatic engorgement and a drowning in their own secretions

The case of the young child deserves special study Here the bechic blast and tussive squeeze are weak and the diameter of the bronchi small

A swelling of the mucosa of 1 mm in an adult bronchus of 10 mm interior diameter would reduce it 36 per cent In an infant, such a swelling in a 2 mm bronchus would reduce it 100 per cent or cause complete obstruction

A realisation of these facts explains the gravity of acute bronchitis or broncho pneumonia in the young, and shows how pulmonary complications are the terminal phase of most deaths in children

Infections—acute and chronic , tuberculosis, mycotic, along with inflammatory mucosal swelling and inflammatory products are among the commonest causative factors

PRE- AND POST OPERATIVE MEDICATION

The two drugs in commonest usage for this purpose are morphine and atropine in combination These drugs exert their main action in two ways —

(1) To reduce the normal glandular secretion and by so doing increase the cohesiveness and adhesiveness of the secretions—adhesive masses forming within the bronchus

(2) By suppression of the cough reflex, peroral pulmonary drainage being abolished

The result is that these abnormal secretions lying stagnant within the bronchus give rise to bronchial obstruction and atelectasis

As early as 1904 Chevalier Jackson demonstrated the dangers of the indiscriminate use of these drugs—how little heed has been paid to his teaching

Pre- and post-operative medication must not be judged by rule of thumb, but individually, for each patient , taking into consideration the age, type of operation, whether post-operative bleeding may occur and involve the upper air passages or affect the upper abdomen with diaphragmatic interference

Prolonged operations with suppression of the cough reflex will favour the formation of obstructive plugs by the accumulation of pathological bronchial secretions

Failure to utilise pre- and post-operative direct laryngoscopic aspiration of these secretions is an important factor in the production of bronchial obstruction and its sequelæ which previously were termed post-operative pneumonia

The avoidance of these complications is no longer in the domain of the surgeon but of the anæsthetist, whose duty it is to maintain a clear airway to the lungs before, during, and after the operation

The importance of a correct post-operative posture cannot be overstressed, dorsal recumbency favouring the development of bilateral bronchial obstruction, especially of the posterior segments of the lung , while prolonged lying on the same side favours obstruction of the lobar and segmental bronchi of the dependent side

Treatment of bronchial obstruction is, of course, based upon the accurate diagnosis of the pathological condition by bronchoscopic examination

Foreign bodies can be removed by forceps, be they inspirated or endogenous in nature

In cases of bronchial obstruction due to the presence of secretions of high viscosity these can be removed by the so-called synergistic bronchoscopic aspiration , this, in fact, means aspiration in co-operation with the tussive squeeze The aspirator removes the secretions, each time it is expelled by the tussive squeeze, from the periphery of the lung into the larger bronchi and before it can be inspirated again by the deep inspiration following a cough

In the early stages and as a prophylaxis before any of the smaller bronchi have been blocked and atelectasis occurred, the use of a gum elastic catheter passed through a laryngoscope down just short of the carina will be sufficient to clear the passages

A word of warning in the young child is necessary , to avoid ballooning the lung by the production of a positive pressure, a tube small enough to allow of the free interchange of air between the vocal cords should be chosen

Where definite signs of atelectasis or emphysema are detected bronchoscopic aspiration will be required

In cases where the obstruction is due to cicatricial stenosis the use of dilators is recommended in preference to endoscopic bronchotomy

PULMONARY ABSCESS

Until the growth of thoracic surgery, bronchoscopic aspiration was the recognised method of treatment, and many were the lives saved by this means

There can be no doubt, however, that many patients are rendered chronic invalids who might have been cured by lobectomy or external drainage

For this reason, therefore, bronchoscopic treatment has fallen into disfavour, and rightly so, in the treatment of chronic lung abscess

Bronchoscopy has a place in the treatment of acute abscess by initiating drainage and allowing the abscess to go on to spontaneous closure and healing

Even in the acute abscesses a watchful eye must be kept on the case to see that improvement is maintained, otherwise further measures must be resorted to, to avoid serious complications ensuing

No case should be treated by bronchoscopy for more than four weeks

BRONCHIECTASIS

What has been said about the bronchoscopic treatment of lung abscess applies in a large measure to bronchiectasis

Its main value now lies as a prophylactic measure, as it can be safely said that if every patient with a slowly resolving infection of the lower respiratory tract received bronchoscopic aspiration the incidence of bronchiectasis would be greatly reduced

In the fully established case, if localised to one side, lobectomy is undoubtedly the treatment of choice

When the lesion is bilateral, or otherwise unsuitable for surgery, benefit may be derived by regular bronchoscopic aspiration of the pathological secretions lying in the bronchiectatic septic tank, thereby rendering the patient's life comfortable, as well as that of his associates

BRONCHIAL ASTHMA

This is essentially a medical problem, but the assistance of the bronchoscopist is often sought to aid in the diagnosis and treatment of the atypical type of case, when the clinical features and symptoms do not conform to what is recognised as " true asthma " and certain conditions that simulate asthma

In this kind of case all types of bronchial obstruction are found, some manifesting a wheezing sound and no dyspnœa

Bronchoscopy is indicated in all recent cases in which there is wheezy respiration, constant or paroxysmal, nocturnal or diurnal

The aphorism of Chevalier Jackson that " all is not asthma that wheezes " must ever be kept in mind

This brings to mind the patient referred recently from the Medical Wards by a very astute Resident She was admitted unconscious with a supposed epileptiform seizure On regaining consciousness the Resident noticed that her respirations were wheezy and that she was developing considerable dyspnœa He considered the possibility of a foreign body and referred her for bronchoscopy

On bronchoscopy a hazel nut was removed from the right main bronchus On questioning the patient later I found that she had been eating hazel nut chocolate before the attack came on

It should be borne in mind that typical slow expiratory respiration occurs in a variety of conditions from a vegetable foreign body in the bronchus to cancer of the lung in the adult

As regards therapy, aspiration will give dramatic relief in many cases by removing the viscid secretions and avoiding obstruction

Aspiration through the aspirating tube passed between the cords is all that is required in most cases

PULMONARY TUBERCULOSIS

Pulmonary tuberculosis was considered for many years one of the main contra-indications to bronchoscopy Now, this is no longer so, and by many it is considered a necessary routine examination before considering collapse therapy By so doing the presence of adhesions and bronchial obstruction can be diagnosed which would otherwise vitiate a satisfactory collapse It would also exclude the presence of pyogenic cocci in the cavity to be collapsed, which, if undiagnosed, might lead to disaster

Its greatest contribution, however, is in the recognition of tracheobronchial lesions which would also interfere materially with collapse therapy

Treatment by silver nitrate application has proved beneficial

From what has already been said it will be evident that the work of a bronchoscopic clinic falls into two main categories

First—The emergency cases involving the removal of foreign bodies from the air passages, or the aspiration of abnormal secretions from the bronchi, be they cases of post-operative collapse or acute medical conditions

For this type of case an emergency service must be provided, available at all times, to the surgical and medical wards of the hospital

Second—The diagnostic work which forms the great bulk of the cases

This can best be carried out in a clinic designed specially for the purpose where there will be the considerable equipment necessary for dealing with the various conditions met with in broncho-pulmonary disease In such a clinic the services of a physician, surgeon and radiologist will be available as members of a diagnostic team

This paper has dealt with the present status of bronchoscopy—what of the future ?

The future of bronchoscopy as I see it, is linked closely with its preservation as an individual science related in the closest way to the sister sciences of laryngology and thoracic surgery, but not absorbed by them

No paper on endoscopy would be complete without reference to the late Dr Ewart Martin whose pioneer work in the speciality will always be remembered in this country I feel very honoured to have trained under him and to have had the privilege of including his figures among those of my own

In conclusion, I would like to express my thanks to Drs Chevalier and C L Jackson and Dr Louis H Clerf, Philadelphia, also Professor McWhirter, Edinburgh, for the help they have given me in the preparation of this paper

BIBLIOGRAPHY

JACKSON, CHEVALIER L , HUBER, JOHN FRANKLIN, *Correlated Applied Anatomy of the Bronchial Tree and Lungs with a System of Nomenclature*

CLERF, LOUIS H , *Progress in Bronchology*

CLERF, LOUIS H , and HERBUT, PETER, *The Role of Bronchoscopy in Diagnosis and Treatment*

NORRIS, CHARLES H , *Early Clinical Features of Bronchogenic Carcinoma*

GIBBON, JOHN H , Jr , CLERF, LOUIS H , HERBUT, PETER A , and DETUERK, J J , *The Diagnosis and Operability of Bronchogenic Carcinoma*

CLERF, LOUIS H , and HERBUT, PETER A , *Diagnosis of Bronchogenic Carcinoma by Examination of Bronchial Secretions*

HERBUT, PETER A , and CLERF, LOUIS H , *Cytology of Bronchial Secretions*

WOOLNER, L B , and MCDONALD, J R , *Bronchogenic Carcinoma Diagnosis by Microscopic Examination of Sputum and Bronchial Secretions*

JACKSON, CHEVALIER L , *Bronchial Obstruction*

JACKSON, CHEVALIER L , and JUDD, A R (1940), " The Role of Bronchoscopy in the Treatment of Pulmonary Abscess," *Journ Thoracic Surg* , **10**, 179

MARTIN, G EWART (1947), " The Position of Broncho-Œsophagology in Great Britain," read before the Section of Laryngology and Otology of the American Medical Association

MARTIN, G EWART (1948), Semon Lecture, The University of London

MARTIN, G EWART (1946), " Presidential Address," Section of Laryngology, Royal Society of Medicine, London

TUCKER, GABRIEL (1949), " Tumors of the Upper Lobe of the Lung Bronchologic Aid in Diagnosis and Treatment," *Ann Oto Rhin Laryn* , **58**, no 4, 1211

OBITUARY

JOHN PATON McGIBBON, M D, F R C P E, D R, D P H

As a result of an accident Dr McGibbon died in Edinburgh on 21st April at the age of 48 He was the son of the late John McGibbon, sometime Professor of Midwifery at the University of St Andrews Early in life he was the victim of a severe attack of poliomyelitis which left him weak and crippled Later he was adversely affected by diphtheria and scarlet fever, and in recent years by chronic laryngitis and bronchiectasis, besides being subject to migraine Such physical disabilities would have daunted most men but not McGibbon, though undoubtedly they influenced his character and career It was thought that his feeble health would preclude him from taking up medicine, so he worked for a time in an office before he took up the study of medicine He qualified in 1929, and acted as resident in medicine and in surgery in the Royal Infirmary and as medical officer at the City Hospital The D P H he obtained in 1932 and later deciding to take up radiology as his specialty he obtained the D R in 1935 The membership of the Royal College he gained in 1933 and he became a fellow in 1937 After a period as assistant radiologist in the Western Infirmary, Glasgow, he returned to work in the Royal Infirmary of Edinburgh By diligent study, logical thought and keen observation he made himself master of his subject in all its aspects, and his opinion was highly valued by those who sought his help His special knowledge and patient study of congenital heart disease were of special value in the diagnosis and treatment of such cases

He took a large share in the teaching in the radiological department and he was a master in the art of exposition His skill came largely from his patience, his humour, his insistence and his ability to appreciate the difficulties of each individual student

Despite his numerous handicaps he had the greatest interest in all forms of sport, and perhaps this was the keynote of his character He revelled in fair play, but reacted most vigorously and fearlessly to any sign of meanness, selfishness, personal greed or aggrandisement He was modest in achievement and had all the qualities of the sportsman courage in adversity, endurance and perseverance despite physical burdens which would have crushed any ordinary man, and loyalty of the highest degree He did not make friends easily but those who were lucky enough found in him a friendship of a rare excellency His subtle sense of humour and the richness of his character made him delightful and inspiring company

McGibbon was a shining example of the power of man to overcome the greatest difficulties, and his character and devotion to duty have been an inspiration to many His loss will be widely felt

ANDREW EDWIN HUNTER, M D

IN the passing of Dr A E Hunter on 1st July, Falkirk loses one of its best-loved personalities

If a living and enduring monument to his memory be necessary, surely it must be the Infirmary, for he was the genius of the place From that tentative beginning, thirty-five years ago, when he undertook to act as visiting physician and surgeon for a trial period of some months in the old building in Thornhill Road, he has watched over its growth and rejoiced in its success How many realise that, for almost thirty years, all the emergency surgery of the district was performed by Dr Hunter ? In spite of heavy calls upon his time and energies, he never overlooked the urgent claims of his busy private practice During these crowded years he was an inspiring teacher to nurse and doctor alike, and many will remember with pride and thankfulness his interest and encouragement

His help as Consultant was frequently sought by his colleagues in family practice, and he was never too busy to answer these requests His colleagues understood what it was to be strengthened by his fortitude, comforted by his wisdom, and cheered by his high-hearted happiness His complete absorption in his duty left him little time to cultivate outside interests, yet his was a many-sided genius, and he might have made a distinguished contribution to the cultural life of the community Only his colleagues were permitted on rare occasions to enjoy his diverse gifts , and his appearances at the Falkirk and District Medical Society were illuminated by grace and wit, choice phrase and speech above the ordinary range

He measured his life by the Golden Rule, a deep unswerving loyalty to the ideals of his profession, without care for his own reputation or gain, and indifferent to popular acclaim or criticism so long as his own exalted conception of duty were fulfilled

NOTE

Royal College of Surgeons of Edinburgh

AT a meeting of the Royal College of Surgeons of Edinburgh held on 21st May 1952, Professor Walter Mercer, President, in the Chair, the following who passed the requisite examinations were admitted Fellows:—Suleiman Abul-Husn, M.D. UNIV. BEIRUT 1945; David Hobson Biggs, M.B., CH.B. UNIV. CAPE TOWN 1943; Charles Bruce Cornish, M.B., CH.B. UNIV. NEW ZEAL. 1947; Ronald Patrick Cumming, M.B., CH.B. UNIV. ABERDEEN 1945; Basil Manfred de Saxe, M.B., B.CH. UNIV. WITWATERSRAND 1945; Amy Dhunjibhoy Engineer, M.B., B.S. UNIV. BOMB. 1938, M.D. 1943; Wilfrid Grundill, M.B., B.CH. UNIV. WITWATERSRAND 1944; Rahman Habib-Ur, M.B., B.S. UNIV. PUNJAB 1946; Jeremiah Dominick Hennessy, M.B., CH.B. NAT. UNIV. IREL. 1945; Jagat Singh Karanwal, M.B., B.S. UNIV. LUCKNOW 1942; Alexander Marshall, M.B., CH.B. UNIV. GLASG. 1945; Jittoo Manoo Mehta, M.S. UNIV. BOMB. 1948; Allin Herbert Moore, M.D. UNIV. MANITOBA 1944; Herbert Dick Rawson, M.B., CH.B. UNIV. NEW ZEAL. 1947; Theodore Francis Redman, M.B., CH.B. UNIV. MANCH. 1940; Alexander Ernest Rublack, M.D., C.M. QUEEN'S UNIV. ONTARIO 1945; Douglas Paviour Short, M.B., CH.B. UNIV. NEW ZEAL. 1946; George Alfred Silley, M.R.C.S. ENG., L.R.C.P. LOND. 1942; Leslie Simon, M.B., CH.B. UNIV. EDIN. 1947; Perin Ratansha Toddywala, M.B., B.S. UNIV. BOMB. 1947, M.D. 1949; Donald Mark Whitley, M.D. UNIV. MANITOBA 1942.

NEW BOOKS

Untoward Reactions of Cortisone and ACTH. By V. J. DERBES and T. E. WEISS. Pp. vii+51. Oxford: Blackwell Scientific Publications. 1951. Price 8s. 6d. net.

This little book, the 131st publication in the American Lecture Series, reviews the vast literature on Cortisone and ACTH listing and describing the manifold undesirable effects which may be produced by these hormones. It contains 96 references and is a concise and efficient guide for the many who should know the dangers but have little time to cull them from the original papers. It emphasises the possibility of avoiding undesirable effects by careful attention to detail and selection of patients. The interdiction of these agents in the tuberculous (p. 40) should not obscure the prime indication for the use of Cortisone in Addison's disease.

Color Atlas of Morphologic Hematology. By G. A. DALAND, B.S. Edited by T. H. HAM, M.D. Pp. v+74, with 14 coloured plates and 9 figures. Harvard University Press. London: Geoffrey Cumberlege. 1951. Price 32s. 6d. net.

The author is an expert technician in hæmatology, and the editor a professor of medicine. The basis of this study is a series of films stained with Wright's stain which gives particularly beautiful results. The coloured reproduction of the blood cells has been excellently done. Each plate includes a large number of typical cells selected from slides, and shown separately so that they can be fully studied. Bone marrow cells are illustrated in so far as they may appear in the circulating blood. There is in addition a useful text, describing the features to be looked for in each disease and the significance of the various findings present. The book covers all the ordinary diseases of the blood and should be of the greatest value as an aid to the recognition of the various disorders. Considering the high standard of its production the price is very reasonable.

The Kidney Structure and Function in Health and Disease By HOMER W SMITH Pp xxii+1049, with 153 illustrations London Oxford University Press 1951 Price 100s net

Past discussions of the function of the kidney have been largely limited by the rival theories of tubular absorption and excretion The result of this controversy has been to focus attention on the excretory function to the exclusions of the equally important role as regulator of the blood content, electrolytic and organic The work of recent years has been of wider conception and has led to the establishment of the part truth contained in each of the rival theories and to the fuller understanding of the high complexity of the kidney function

Homer Smith's *The Kidney* is rightly accepted as the leading modern textbook of renal physiology Discarding the theoretical discussions of the past for the wider knowledge of the present time, it enters into every detail with clarity so that even the difficult complex clearances are readily understood It is not a book for those in search of elementary physiology, it requires a full basic knowledge for appreciation of its value

The subtitle indicates that it is a book of practical application The clinician will value it as highly as the physiologist Though pathology is but little dealt with, the present physiological views are ably applied to renal diseases and also to the effects of general diseases on the kidney

A bibliography of 2300 references is indicative of the extent of the study

Physical Medicine and Rehabilitation for the Clinician Edited by FRANK H KRUSEN, M D Pp xv+371, with 93 illustrations London W B Saunders 1951 Price 32s 6d

One of the axioms enunciated in this book is that the physician should prescribe physical methods of treatment with the same accuracy as he does potent drugs In order to do that he must know the rationale of physiotherapy with its limitations and contra-indications This is a textbook from which clinicians would derive considerable help and it would enable them to relieve the physiotherapists from a great deal of unnecessary work and so let them give more satisfactory treatment to those who require prolonged sessions Study of this book would give the doctor confidence in explaining to the querulous patient whether physiotherapy would be beneficial or of no value There are forms of treatment which the doctor or the patient can carry out efficiently if sufficiently instructed and there is no need to go beyond this book for advice on the subject Study of this volume would repay the time spent

Decompression Sickness Caisson Sickness, Divers' and Flyers' Bends and Related Syndromes By JOHN F FULTON, M D Pp 437, with 88 figures London W B Saunders 1951 Price 42s 6d net

Compressed air illness or caisson disease is an occupational malady suffered by men who work in increased atmospheric pressures It is caused by the vaporisation of nitrogen from the blood as a result of too rapid or incomplete decompression Bubbles of gas present in the blood stream or tissues give rise to joint pains—" the bends "—abdominal cramps and other symptoms

High altitude flyers may suffer from a similar condition due to the escape of dissolved nitrogen from the blood in a rarefied atmosphere In 1942 a sub committee of the National Research Council undertook the study of " Decompression Sickness " as it affected flying personnel This work has resulted in much new knowledge of the disease which is here recorded

This book should be a useful reference work for the general medical reader, while the doctor in industry and particularly the Air Force Medical Officer, will find it a valuable addition to his library

Ear, Nose and Throat Diseases for the General Practitioner By WILLIAM MCKENZIE, M B , B CHIR , F R C S Pp 136 Edinburgh E & S Livingstone 1952 Price 9s net

The form of this book suggests that it presents material from a short series of lectures The first person singular recurs with irritating frequency While allowance must be made for dogmatism in a work of this nature, exception could be taken to too many of the views expressed It is definitely not for undergraduates

The Use of Tracer Elements in Biology By W E OVEREND, PH D Pp iv+57 London Heinemann 1952 Price 3s 6d

The object of this series is to make available recent advances of knowledge which have not yet reached the textbooks After a short introduction the author discusses the requirements for a tracer then goes on to describe the uses that have been made of tracers in biology His final chapter on tracers in medicine is very stimulating and suggestive This subject has a great future and every medical man should be familiar with its possibilities

The English Pioneers of Anæsthesia By F F CARTWRIGHT Pp x+338, with 20 plates Bristol John Wright 1952 Price 21s

In this small volume Dr Cartwright, Anæsthetist at King's College Hospital, London, has written three excellent biographical studies of Thomas Beddoes, Humphry Davy and Henry Hill Hickman Being himself of West of England stock and with forebears who had intermingled socially with Beddoes and Hickman, the author, not unnaturally, has had some additional stimulus to give vitality to his story As a result of considerable research some new material has been elicited and certain mistaken conceptions concerning the original work of the three pioneers have been corrected The thesis that their contributions to the development of anæsthesia have been underrated in the past is well sustained in a scholarly presentation of the scientific evidence against a background of personal histories which continuously holds the interest of the reader Dr Cartwright's book is worthy of a place on the bookshelves of all doctors whatever their particular sphere of activity may be

The Advance to Social Medicine By RENE SAND Pp 590, with an index London Staples Press 1952 Price 42s net

In this book Professor Sand not only describes the history of social medicine itself but gives a detailed account of the converging streams of medical thought and practice which have produced the broad flow of preventive medicine which we know to-day There is no field upon which he does not touch, and he mentions most of the great medical figures of the past two thousand years and many earlier still It is interesting and salutary to learn that some " modern discoveries " and recent health machinery are indeed old , for example, the sixteenth century health offices maintained in French cities to deal with epidemics, and the belief widely held in Africa and the East since earliest times that malaria was caused through a mosquito bite

This compendious volume is packed with information , in fact, so rich a fare is offered that the book is one to dip into rather than to read straight through In places the style suffers from over condensation, and this may also account for certain inaccuracies in the text In the chapters dealing with contemporary preventive medicine, there are numerous references to the U S S R with, unfortunately, no details given, and the section devoted to international contributions to social medicine is inadequate Nevertheless, this book is an important contribution to the history of medicine in general and social medicine in particular

NEW EDITIONS

The Pharmacologic Principles of Medical Practice By JOHN C KRANTZ and C JELLEFF CARR Pp xvii+1116, with 95 figures Second Edition London Baillière, Tindall & Cox 1951 Price 76s 6d

A new edition of this essentially practical American textbook has been called for after a period of only two years As before, the arrangement of the subject-matter is based upon the physiological systems of the body, and the emphasis is placed on currently used drugs The mechanisms of their actions and their clinical application are fully explained and discussed Although the official American names differ in some cases from British ones this does not give rise to any great difficulty, and the book should prove both interesting and useful to students and medical teachers

Obstetrical Practice By ALFRED C BECK, M D Fifth Edition Pp xiv+1073, with 947 illustrations and 22 reproductions of X-ray films London Baillière, Tindall & Cox 1951 Price 76s 6d net

Much of this edition has been rewritten so as to incorporate the relevant new physiological and pathological knowledge and present the modern changes in opinion regarding the management of some obstetrical problems The extensive bibliography at the end of each chapter shows the wide and varied reading which the author has moulded into his own experience and practice The text is clear, reads easily and is liberally illustrated, indeed the mechanisms of labour and many of the operative procedures are depicted in a series of simple drawings executed by the author, and make for clarity of teaching and avoidance of lengthy descriptions An interesting feature of the book is the reproduction of portraits of eminent obstetricians found at the and of many of the chapters

The physiology of the fœtus is described in detail, but with the exception of asphyxia, and the initiation of lactation, little reference is made to the newborn child and the commoner pathological conditions met with after birth There is also little to be found on the vexed question of postmaturity apart from its occurrence in diabetes To avoid confusion the reader in this country must remember that the definition and use of " presentation " is the traditional American one and corresponds to the British use of " fœtal lie "

A Clinical Atlas of Blood Diseases By A PINEY, M D, M R C P Seventh Edition Pp vii+137, illustrated London J & A Churchill 1952 Price 21s net

This Atlas which first appeared in 1930 has long been regarded as a standard work The essential features of the book is a series of 48 full-page illustrations, 45 of which are in colour With each illustration is a short account of the disease covering all the important features A further series of descriptions is given of conditions not illustrated The work is beautifully produced and should be of the utmost assistance in the differentiation of blood disorders

The Asthmatic Child By G F WALKER, M D, F R F P S G, D C H, M R C P Second Edition Pp 19, with 24 illustrations Bristol John Wright 1952 Price 2s 6d

This small brochure is addressed to the parents of asthmatic children Two pages of general instructions are followed by a description of ten different exercises illustrated by a series of photographs A useful publication

Introduction to Clinical Neurology By GORDON HOLMES, M D, F R S Second Edition Pp viii+189, with 43 illustrations Edinburgh E & S Livingstone 1952 Price 12s 6d

From his vast experience as a clinical teacher the author has produced a book which outlines the essential background on which alone it is possible to build a proper understanding of nervous disorders

It is a book of symptoms and signs, and their explanation and significance in relation to present-day anatomical and physiological conceptions, and in this edition only a few additions have been required due to the increase in knowledge of these basic subjects

Methods of clinical examination receive a prominent place and many useful practical points are to be found Wisely, too, all mechanical aids to diagnosis have been excluded, impressing on the reader the importance of clinical methods founded on the basic principles so masterfully presented here

Internal Medicine Its Theory and Practice By J H MUSSER, B S, M D, F A C P Fifth Edition Edited by M G WOHL, M D, F A C P Pp 1503, with 236 illustrations and 10 coloured plates London Henry Kimpton 1952 Price 105s net

This edition, like its predecessors, presents in one volume a comprehensive survey of the entire field of internal medicine Many new subjects such as genetics, geriatrics, rehabilitation, psychosomatic disorders and the general adaptation syndrome are included in this latest edition Over eighty authors have contributed sections in their own special branch of medicine This book can be thoroughly recommended to both student and post graduate

The Practitioner Handbooks Practical Procedures Edited by SIR HENEAGE OGILVIE, K B E, D G, G C R, F R C S, and WILLIAM A R THOMSON, M D Second Edition Pp 380 London Eyre & Spottiswoode 1952 Price 25s net

Although this book is technically a second edition it has undergone such thorough revision and complete resetting that it is practically a new book Many new chapters have been added, dealing with such subjects as the administration of antibiotics, hormone implantation therapy, biopsy, and gynæcological and ophthalmological procedures This book povides sufficient detail of common procedures to allow the practitioner and hospital resident to carry them out or to know what is required if they are to be done by someone else Furthermore, it explains in detail the rationale of some procedures and should therefore prove of great value to practitioner and hospital resident alike

Approved Laboratory Technique By J A KOLMER, M D, SC D, D P H, F A C P E H SPAULDING, PH D, and H W ROBINSON, PH D Fifth Edition, with 403 illustrations and 28 coloured plates London H K Lewis 1952 Price 90s

In preparing this work the authors have had the assistance of a team of 18 experts This new edition is considerably enlarged and in great part rewritten It covers all fields of clinical laboratory work, bacteriology, serology, pathology and chemistry, including the detection of certain poisons Methods are described in great detail since no laboratory examination can be better than the thoroughness and skill with which it is conducted The authors also emphasise the care with which the clinician should take the specimen, and again describe in considerable detail the proper methods for collecting material for investigation

The book is a thoroughly sound and authoritative guide to laboratory examinations and can be highly recommended

BOOKS RECEIVED

The Tissues of the Body By W E LE GROS CLARK, F R S Third Edition Pp xi+407, with 124 illustrations Oxford Clarendon Press 1952 Price 30s net

The subject of anatomy is apt to be regarded merely as a study of topography—a description of the structural complexity of mature organisms Professor Le Gros Clark, however, in *The Tissues of the Body*, rightly emphasises the importance of the teaching of structural organisation as a dynamic process He stresses the relationship of structure to function, and frequently alludes to recent experimental investigations The sections on vascular patterns, muscle architecture, and mechanics and growth of bone are particularly interesting He states that in this introduction to the study of anatomy he has endeavoured to provide intellectual stimulation, and he succeeds brilliantly

BOOKS RECEIVED

ARMSTRONG, HARRY G, M D, F A C P Principles and Practice of Aviation Medicine *(Baillière, Tindall & Cox, London)* 57s 6d net

ARMSTRONG, J R, M D, M CH, F R C S Lumbar Disc Lesions *(E & S Livingstone Ltd, Edinburgh)* 42s net

BARRON, S L, and SCHOTT, A, M D (HEIDELBERG), M R C S Cardiographic Technique *(William Heinemann, London)* 21s net

BRITTAIN, H A, O B E, M A, M CH, F R C S Architectural Principles in Arthrodesis Second Edition *(E & S Livingstone Ltd, Edinburgh)* 42s net

FLOREY, M E, M D The Clinical Application of Antibiotics Penicillin *(Oxford University Press, London)* £4, 4s net

GARDNER, ERNEST, M D Fundamentals of Neurology Second Edition *(W B Saunders, Company, London)* 24s

GRAY, JAMES, M A, F R S E History of the Royal Medical Society, 1737 1937 *(The University Press Edinburgh)* 42s net

Edited by GUTHRIE, DOUGLAS Logan Turner's Diseases of the Nose, Throat and Ear *(John Wright & Sons, Bristol)* 42s post 1s 1d

LÉPESCHKIN, EUGENE, M D Modern Electrocardiography The P Q R S T U Complex *(Baillière, Tindall & Cox, London)* 9s 6d net

LEYTON, NEVIL, M A (CANTAB), M R C S, L R C P Migraine and Periodic Headache *(William Heinemann, London)* 12s 6d net

MAINLAND, DONALD, M B, CH B, D SC, F R S E, F R S C Elementary Medical Statistics *(W B Saunders Company, London)* 25s

MAXIMOW, ALEXANDER A, and BLOOM, WM A Textbook of Histology Sixth Edition *(W B Saunders Company, London)* 50s

Edited by MILLER, SEWARD E, M D A Textbook of Clinical Pathology Fourth Edition *(Baillière, Tindall & Cox, London)* 68s 6d net

PAUL, HUGH, M D, D P H The Control of Communicable Diseases *(Harvey and Blyth Ltd, London)* 55s

SALTER, WILLIAM T, M D A Textbook of Pharmacology *(W B Saunders Company, London)* 75s

SCOTT BROWN, W G, C V O, M D, B CH, F R C S Diseases of the Ear, Nose and Throat Volume I *(Messrs Butterworth & Co Ltd, London)* £8, 8s per set

Edited by SCOTT BROWN, W G, C V O, M D, B CH, F R C S Diseases of the Ear, Nose and Throat Volume II *(Messrs Butterworth & Co Ltd, London)* £8, 8s per set

Surgical Forum Committee Surgical Forum *(W B Saunders Company, London)* 50s

TIDY, NOEL M Massage and Remedial Exercises in Medical and Surgical Conditions Ninth Edition *(John Wright & Sons Ltd, Bristol)* 27s 6d

WELLS, CHARLES Prostatectomy A Method and its Management *(E & S Livingstone Ltd, Edinburgh)* 24s net

Edited by WILLIAMS, P O, M A (CANTAB), M B, B CHIR, M R C S, L R C P Careers in Medicine *(Hodder & Stoughton Medical Publications, London)* 15s net

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SURGICAL EMERGENCIES OF INFANCY

By F H ROBARTS, M B, F R C S Ed
Assistant Surgeon, Royal Hospital for Sick Children, Edinburgh

INTRODUCTION

" I PRESUME not to write of things which I never had an experience of—those I leave unto wiser men " These words were written by Felix Wurtz, a Swiss surgeon of the sixteenth century and author of *The Children's Book*—the first treatise on Infantile Surgery

I too intend to refer only to those things of which I have had experience There are few surgeons in this country who are concerned with the surgery of the infant and the child alone, and many general surgeons, on occasion, are faced with the problems of surgery in the infant, the clinical approach to which differs considerably from that in the adult

The broad headings for the conditions which will be discussed are as follows —

A *Congenital deficiencies of the parietes of the body cavities*
  (1) Of the abdomen
  (2) Of the cranium and the vertebral canal

B *Alimentary conditions*
  (1) Obstructions
  (2) Obstruction with fistulous communications
  (3) Obstructions sometimes associated with hæmorrhage from the bowel
  (4) Hæmorrhages from the bowel sometimes associated with obstruction

C *Infective conditions*

D *Genito-urinary emergencies*

E *Foreign bodies in the natural passages of the body*

Traumatic conditions have been omitted purposely first, because the infant is less often exposed to injury, secondly, because treatment differs little from that founded on basic principles and applied to all ages

A Honyman-Gillespie Lecture delivered in Edinburgh on 1st November 1951

GENERALITIES

Before approaching the clinical and technical aspects of surgical emergencies in infancy, it may be profitable to mention some *important generalities*

History and Clinical Examination —In adults, the history is obtained directly The infant is often brought to hospital by a junior nurse, by an obliging but ill-informed neighbour, or by an anxious grandmother Mothers vary in intelligence and composure The doctor's letter seldom contains all the information desired Records from other hospitals should be invaluable, but only if accurate and truthful Therefore the data of a history have to be sifted with considerable care, and every detail of the clinical examination assumes great importance Co-operation from an infant is entirely lacking and although there should be method, opportunities must be seized quickly as they occur If it is causing distress to an ill child the examination must be brief though punctilious Firm decisions are desirable Diagnostic doubts are seldom resolved by continued examination, and searchings for further signs portend greater confusion These are general principles whose importance is enhanced for the pædiatric surgeon

Radiological Investigation —The chief ancillary to the clinical examination is an appropriate radiological investigation This procedure is particularly helpful in the alimentary obstructions Straight " scout " films of the abdomen are preferable, for they cause little upset to the child Sometimes it is imperative that a contrast medium should be used Vomiting and regurgitation endanger the infant with obstruction by aspiration of the vomit into the lungs, where barium sulphate produces a severe and often fatal pneumonia Lipiodol, in minimal quantities, is satisfactory and eliminates this risk As a " follow-through " medium in cases of doubtful obstruction it can be a very useful agent

In cases of spina bifida, which by the clinical examination may have been adjudged suitable for operation, an X-ray of the skull will often show the lacunar areas of bone porosity which attend a degree of hydrocephalus This is a feature which precludes a satisfactory outcome from operative correction of the spinal deformity

Vomitus —Certain bed-side and side-room examinations are also of considerable value in diagnosis An inspection of the vomitus is always of interest In congenital hypertrophic pyloric stenosis the absence of bile is a useful sign , of greater importance are the amount of the gastric residue and the time relationship of the specimen to the previous meal The amount of mucus in the specimen is an indication of the severity of the accompanying gastritis This influences the nature of the pre-operative treatment In duodenal atresia and volvulus neonatorum, frequent vomiting of a bile-stained fluid in association with visible gastric peristalsis occurs In all obstructive states gastric suction is an indispensable safeguard against asphyxia, pneumonia and atelectasis

Meconium and Stool—An examination of the stool or of material obtained on rectal examination is of interest and importance Even in intestinal atresia a considerable quantity of meconium may be passed and this may be little changed in appearance from the normal, though usually it is less bulky, paler and more inspissated When the alimentary tract is entirely patent vernix cells from amniotic fluid swallowed *in utero* are always found in meconium In intestinal atresia they are not demonstrable in a suitably stained smear preparation (Farber, 1933) Blood and mucus, both in moderate quantity and without fæces are found typically in the majority of cases of acute intussusception Blood in quantity without mucus suggests enteric ulceration such as may occur in association with a Meckel's diverticulum, with heterotopic islets of gastric mucosa, or it indicates intestinal duplication Blood with a foul stool and severe toxæmia may occur in acute gastro-enteritis, and blood in association with bruising may point to an acute scorbutic condition or hæmophilia

Pre-operative and Post-operative Care—In recent years considerable advances have been made in measures for the pre-operative and post-operative care and sustenance of infants However, it is quite true that an infant who is full-term, strong and healthy in all respects other than its congenital anomaly, will tolerate operative intervention of a major degree Once this initial advantage has been lost by delay, and the temporary decline of the first week of life and the effects of an anomaly allowed to develop to a severe extent, this resistance to trauma, developed for the supreme stresses of birth, disappears

The fluid and electrolytic balances of an infant are rapidly disordered by dehydration and over-hydration Great care must be exercised in parenteral administrations of fluids, with a total blood volume in the new-born of only 300 to 400 c c, or in the child of a year of 600 c c, overloading can easily occur The daily fluid requirements of such infants are in the region of 450 and 1000 c c respectively As a general rule, if a child is in urgent need of fluid, 15 c c per pound of body-weight may be given as an infusion, if blood is required, the transfusion volume can be estimated at not more than 10 c c per pound of body-weight

The value of chemotherapeutic agents both prophylactically and therapeutically needs only to be mentioned In the very young child there is little place for the use of other drugs, but adequate sedation of the older infant is just as important as it is for the adult Heroin gr 1/96 has always been found satisfactory and reliable Phenobarbitone gr 1/2 to 1 produces a lighter and more prolonged effect Hypoprothrombinæmia develops rapidly in any ill child whose natural intake is reduced, the routine administration of vitamin K analogue is desirable for its anti-hæmorrhagic effect and for the ensuring of sound wound-healing

Anæsthesia—The advances of modern anæsthesia and their application by anæsthetists skilled in this work have contributed more than anything else to the improvements in mortality figures, and permit more formidable procedures General inhalation anæsthetics administered with closed-circuit apparatus adapted to the small and feeble respiratory excursion of the infant are most satisfactory Even intratracheal administration and positive pressure with controlled respiration are obtainable for intra-thoracic work, and with care there is little risk of pressure effects upon the delicate tissues of the larynx and the lungs In abdominal work spinal anæsthesia and the relaxant drugs are not considered safe or suitable for the infant

The discussion of these preliminary basic matters is important for it is upon a full understanding of them that the success of any surgical procedure depends

CONGENITAL DEFICIENCIES OF THE PARIETES OF THE BODY CAVITIES

Congenital deficiencies of the parietes of the abdominal cavity are the most important and include the following and related conditions which will require urgent surgical treatment

(1) Congenital umbilical hernia or exomphalos
(2) Irreducible inguinal hernia
(3) Torsion of a testis—usually related to incomplete descent and to association with an inguinal hernia
(4) Torsion or strangulation of an ovary in association with an inguinal hernia

Exomphalos—Exomphalos is a condition which is evident at birth More than the usual care should be exercised in the ligation of the cord so that no content of the hernial sac is ensnared By inspection of the transparent sac the nature of its visceral content can be made out A large amount of visible liver and a broad base of over 7 cm will suggest that difficulty may be encountered in obtaining sound closure at the initial attempt Provided that no other serious congenital anomaly exists, operation should be performed at the earliest opportunity, with delay, the amniotic covering dries and is more liable to rupture, the alimentary tract becomes filled with swallowed air and closure becomes more difficult Disaster will come with attempts to pack viscera tightly into the small abdominal cavity It is dangerous to deepen the anæsthesia to assist in this process If the fascial edges and peritoneum cannot be united easily, further dissection of the skin and superficial tissue will allow of their approximation, the large mural defect which remains being repaired secondarily after the lapse of two to three weeks when the abdominal cavity has enlarged (Gross and Blodgett, 1940) Then there is no longer any danger of causing cardiac and respiratory embarrassment or intestinal obstruction by the production of undue intra-abdominal pressures When the defect is large it has been suggested that no attempt should be made to excise the hernial sac The coverings are rendered as sterile as possible by bland antiseptics and the skin is widely mobilised from around the point of junction with the sac, which can then be covered entirely by this skin Thus adequate protection is obtained until a second operation for the repair of the very large umbilical hernia is performed (Gross, 1948)

Irreducible Inguinal Hernia—Inguinal hernia from patency of the processus vaginalis is of very common occurrence To a lesser extent is such a deficiency found in respect of the canal of Nuck in the female Irreducibility of hernial content occurs in a proportion of these cases The term " irreducibility " is used advisedly for strangulation of bowel is unusual though not unknown This complication occurs more often in the premature child and sometimes at the first appearance of the hernia Under the age of three months delay is desirable in advocating operative treatment of the uncomplicated inguinal hernia for spontaneous cure may occur Irreducibility is an indication for more immediate operation The actual diagnosis of the condition seldom presents much difficulty, but a tense and encysted hydrocele of the cord may simulate it It is usually possible to feel the upper limit of a hydrocele in the cord If there is any uncertainty, in cases of irreducible hernia it will be found that tender enlargement of the corresponding testis has occurred from interference with its venous return Considerable œdema of all the cord structures below the obstruction occurs rapidly, and in tissues which are already often tenuous and delicate, this is a change which makes definition of the sac at operation more difficult It is because of this that attempts to obtain spontaneous reduction should be made Direct taxis is seldom successful, distresses the child and may be dangerous Sedation with chloral hydrate gr 2 to 5, according to age and size, is the most important factor in obtaining reduction This may be assisted by raising the foot of the cot, by flexing the thigh on the affected side, and by the application of warmth Should these methods fail after two hours' trial, operation becomes essential When they succeed, a short delay is permitted for the absorption of œdema, and operation is performed before the child goes home Some irreducible herniæ undergo spontaneous reduction, or can be reduced manipulatively under the general anæsthetic , the operation can then be carried out as for the simple case, without opening the inguinal canal At this age the irreducible hernia differs from that in the adult in that the obstructing agent is usually the external and not the internal inguinal ring If the irreducible state persists, an obliquely placed incision becomes necessary so that the external oblique aponeurosis can be exposed, the canal opened and the constricting external ring divided from above downwards The usual precautions must be taken to secure the hernial content for inspection of its viability before it is allowed to return within the abdominal cavity The hernial sac is then excised in the usual manner, though this may be difficult in the vaginal type where the testis dangles from its mesorchium within the sac and the vas and vessels appear to be an integral part of its wall It is this type which is often encountered in the premature child

Torsion of the Testis —It is the vaginal type of hernial sac which so often accompanies undescent of the testis, and such a testis hanging by its mesorchium in this potential space is the one in which torsion may occur The abnormal position with consequent exposure to external forces and to the stresses of muscular contractions are the factors which produce torsion The onset of symptoms is sudden, and examination reveals a tender lump in the region of the external inguinal ring or of the canal itself The testis is absent from the scrotum, as may be its fellow also , if the testis is more fully descended it is painful and swollen, but the higher lump of an irreducible hernia is absent The differentiation from an acute epididymo-orchitis then arises, and if any doubt exists it is safer to operate Unless the torsion is undone within a few hours of its onset, irreversible changes in the testis occur which make orchidectomy necessary With bilateral undescent of the testes in which torsion on one side and subsequent orchidectomy have occurred, there is a risk that similar events may occur in the remaining testis At this stage it is often found impossible to bring that testis down into the scrotum any attempt to achieve this may cause testicular atrophy The minimum of operative disturbance is desirable, and it is recommended that even cure of the hernia be left until a later date, but that the mobile testis be immobilised by " button-holing " it through the wall of the sac and the coverings of the cord in the position where it already lies

In the female, similar complications of an inguinal hernia may arise An ovary may prolapse, become incarcerated and even strangulated, or may undergo torsion Such incidents are corrected by the same methods which apply to the male

CONGENITAL DEFICIENCIES OF THE CRANIUM AND VERTEBRAL CANAL

Spina Bifida —Of the anomalies which affect the skull and vertebral canal the degrees of spina bifida are the commonest In the past, valiant attempts to repair these defects have been made Usually meningoceles with a small defect were and still are amenable to surgical correction , where nerve tissue is present outside the spinal canal, as in the commonest degree of myelomeningocele, it is seldom possible to effect a cure which will remain satisfactory Even where there does not appear to be any paresis of the lower limbs or urinary or anal incontinence and no obvious or radiological signs of hydrocephalus, some if not all of these features will almost certainly appear eventually, leaving the child an uneconomic responsibility to the parents or to the community Unless the type of the deformity is simple and uncomplicated surgical correction is not advised

ALIMENTARY ANOMALIES

It is the anomalous conditions of the alimentary tract which provide the greatest variety of surgical emergencies of infancy Acute intussusception is not rare, and although it is an acquired condition, in some cases, there are minor anomalies which seem to contribute to its development Other acquired conditions of this system are all relatively uncommon

INTESTINAL OBSTRUCTIONS

This group includes —

(1) Congenital hypertrophic pyloric stenosis
(2) Intestinal atresia and stenosis
(3) Intestinal malrotations and volvulus neonatorum
(4) Meconium ileus
(5) Hirschsprung's disease
(6) Imperforate anus

Congenital Hypertrophic Pyloric Stenosis—In cases of congenital hypertrophic pyloric stenosis, the details of history and clinical findings are well known Gastric peristalsis is not pathognomonic of the condition It is always desirable to palpate the pyloric tumour before deciding upon operation It is not always felt easily, sometimes it is relaxed More frequently, the large and hypertrophied stomach overlies the tumour and masks it The tumour never feels as large as it is found to be at operation Operative treatment is now almost universally accepted by pædiatricians This should be carried out within twenty-four hours of the diagnosis having been established, unless the child is very unfit and requires longer for the correction of its metabolic disturbances and amelioration of its gastritis by lavage Rammstedt's operation leaves nothing to be desired in its effectiveness Accidental opening into the duodenum is an event which will happen to most surgeons at some time, the possibility can be lessened by the meticulous termination of the initial pyloric incision at the distinct lower limit of the tumour and by gripping the duodenum immediately below the tumour, evaginating it from the duodenal fornices while the incision and the muscle separation are being performed The operative mortality is now very low as a result of the appreciation by pædiatricians of the value of early operation and of better preparation for operation Also of great importance are the more general use of light inhalation anæsthesia in support of regional local infiltration, and isolation from the risks of respiratory and alimentary infections

Atresia and Stenosis of the Intestines—Atresia and gross stenosis of the gut produce obstructive symptoms within the first days of life Minor degrees of stenosis seldom present as urgent conditions The site of the lesion modifies the symptoms and the clinical findings the higher, the more acute is the onset, and the more rapid the deterioration, less evident are distension, ladder patterning and visible peristalsis Straight films of the abdomen are of great help in assessing approximately the level of the obstruction, and usually aid in distinguishing these cases from obstruction due to a volvulus of the mid-gut loop The vernix test upon the meconium is an additional help

The treatment of these anomalies must be operative and mortalities are still very high It is important to remember that the lesions are not infrequently multiple and a thorough search of the whole gut is necessary Gross distension renders this inspection difficult, and evisceration is justifiable in order that time may be saved and mistakes avoided Decompression of dilated loops by large-bore needle puncture and suction may be required for the replacement of the coils within the abdomen The obstruction must be overcome by anastomosis, in the upper half of the duodenum by gastro-jejunostomy, and in its lower half by that procedure or, preferably, by duodeno-jejunostomy In the infant entero-anastomosis should if possible be done by the end-to-end or end-to-side techniques Although great care may be taken to keep the blind loops of a side-to-side junction as short as possible, with normal growth they can increase to form considerable cul-de-sacs, especially on the proximal side These may cause troublesome symptoms in later life In the circumstances of atresia direct end-to-end anastomosis is quite impracticable because of the marked difference in calibre of the loops to be united Decompression of the proximal loop by puncture or enterotomy may reduce this to some extent It is in the minute distal loop that most trouble is encountered Its lumen is very small and suturing can reduce this dangerously Its calibre can be increased artificially by injection of saline or air into it through a hypodermic needle Anastomosis in two layers is not always possible, and it may be necessary to be content with one layer of interrupted silk sutures, which will allow free growth of the stoma

These technical difficulties and the poor healing qualities of the proximal loop, whose viability is impaired by distension and partial volvulus, make disruption of the suture line a frequent complication Resection of the proximal loop secures healthier bowel of greater strength and of more equal calibre for an anastomosis Resection also removes a considerable amount of tenacious bowel content which can perpetuate the obstruction in the contracted distal bowel after anastomosis

If there are several zones of atresia, the anastomosis will be performed with the first unobstructed portion of bowel The atretic closed loops which have been by-passed should be left to be removed subsequently, they will cause no immediate trouble, though they may well do so by distension if allowed to remain indefinitely Where the occlusion is by a diaphragm across the lumen of the bowel, it may be practicable to resect the greater portion of this through an enterotomy wound with closure of this transversely

In the immediate post-operative period there is concern for the ability of the hypoplastic bowel below the anastomosis to increase its calibre At operation dilatation may be encouraged by the injection of saline in sufficient quantity to flow round to the rectum , subsequent passage of meconium through this portion of bowel may be encouraged by the injection of mineral oil into the lumen of the gut After operation distension of the large bowel may be further stimulated by saline enemata No mention has hitherto been made of ileostomy for the relief of obstruction This has only an occasional use in the very ill child Temporary improvement may then be obtained, but deterioration will very soon return and further measures for reconstitution of the bowel continuity must be undertaken

Rotational Anomalies—It is well known that acute obstructive states can develop from rotational errors of the mid-gut It is not always appreciated that a dual pathology often underlies the obstruction The incomplete descent and fixation of the cæcum into the right iliac fossa result in an inadequate attachment of the mesentery of the whole small bowel to the posterior abdominal wall The base of the mesentery is short and transverse, for the cæcum lies near the second part of the duodenum Peritoneal reflections pass from the cæcum to the lateral aspect of the duodenum The weight of the mid-gut may be sufficient to drag these peritoneal folds tightly across the duodenum This simple cause of obstruction can operate from soon after birth, but more frequently symptoms of a periodic and less acute nature result When a volvulus of the mid-gut occurs, the obstruction becomes two-fold , the traction across the duodenum is intensified, and the whole mid-gut becomes closed This obstructive mechanism usually operates soon after birth, hence the term *volvulus neonatorum*

Usually within two or three days of birth acute obstructive symptoms from these anomalies become very evident The vomit contains bile, but obvious gastric distension with visible peristalsis may be absent through the efficacy of the vomiting Abdominal distension depends upon the presence of volvulus and the degree of distension of the coils involved , if seen at an early stage these may be collapsed, later to distend with increasing bacterial putrefaction within them Considerable help may be got from a straight X-ray of the abdomen Duodenal distension ceasing abruptly in its second part, and gas in very little or varying amounts in the central area, with evidence of free fluid between the bowel coils, are strong evidence of this obstructive condition

At operation, transverse incisions give excellent access and immediate appreciation of the exact nature of the obstruction is gained from the nature of the presenting coils of bowel If there is much free fluid within the peritoneal cavity and if distended loops of small bowel present, there is a state of volvulus, which requires complete eventration of the child's gut to permit of its rapid reduction and inspection for the probable secondary causes of obstruction around the duodenum itself Reduction is affected usually by rotation of the whole of the mid-gut in an anti-clockwise direction If the colon presents itself on first inspection, there is no volvulus Displacement of the mobile cæcum downwards and to the left exposes the second part of the duodenum Obstructing peritoneal reflections are divided and the cæcum displaced into the left half of the abdomen (Ladd, 1933) If the remainder of the duodenum, now exposed, does not descend directly down the right side of the vertebral column, search must be made in the region of the ligament of Treitz for further extrinsic causes of obstruction These, too, must be divided, either until the duodenum can be made to descend vertically in its remaining parts, or until a Ryle's tube in the stomach can be threaded on into the upper coil of jejunum, where it may with profit be allowed to remain temporarily (Glover and Barry, 1949) These manœuvres result in a relative lengthening and altered axis of the posterior attachment of the mesentery, and are sufficient to ensure against the recurrence of volvulus

Meconium Ileus —The treatment of meconium ileus causes the pædiatric surgeon little satisfaction, first, because of the poor prognosis and, second, because the techniques at operation appear so crude The underlying pathology, which can never be corrected, is a congenital fibro-cystic disease of the pancreas This produces cœliac-like symptoms if the child lives Staphylococcal broncho-pneumonia is a frequent complication on account of similar changes in the bronchial mucous glands In the history the hereditary trait may help to indicate the cause of the obstruction which appears soon after birth The absence of meconium in the rectum, and its replacement by a small yellowish mucus plug, the peculiar hard feel of the abdomen, dull on percussion, and the radiological sign of intra-abdominal calcification are conclusive findings The site of obstruction is usually found in the lower ileum, where there is a sudden change from dilated and hypertrophied obstructed gut to hypoplastic ileum, the proximal few inches of which contain firm nodules of inspissated calcareous material The whole of the large bowel is a " microcolon " Volvulus, necrosis, and perforation of the distal dilated loop are not uncommon The procedure which is usually advocated in order to overcome this obstruction is proximal enterotomy and through a catheter the washing out with saline of the inspissated material after it has been softened and broken up by external pressure Injection of fluid onwards into the microcolon will confirm that the obstruction has been relieved and it will increase the calibre of the bowel for the passage of the tenacious meconium which is present above the actual level of the obstruction (Hiatt and Wilson, 1948) This is not a technically satisfying procedure , therefore, it is suggested that no less success might be anticipated by an anastomotic procedure as in atresia, difficult to perform, but less redolent of a plumber clearing a choked drain The deficient ferment is supplied as pancreatin and is given into the bowel at operation and by mouth and by enemata afterwards

Hirschsprung's Disease —Hirschsprung's disease causes trouble with the bowel function from the earliest days of life, whereas megacolon from other causes is a condition acquired gradually in a gut which has previously functioned well Hitherto attention has been focussed on the dilated portions of the colon Recently it has been shown that the abnormality is situated in a contracted segment of bowel below the secondarily dilated and hypertrophied sections In this hindmost narrow portion there is a congenital absence of the ganglion relay cells of the parasympathetic innervation (Swenson, Rheinlander and Diamond, 1949) Sympathetic predominance, with a failure of relaxation and incapacity for co-ordinated peristaltic activity, exists The extent of the affected segment may vary from involvement only of the lower rectum or it may include the whole of the large gut, and in some cases even the terminal ileum With a long section of the gut involved, obstructive symptoms develop soon after birth , whereas in the less affected cases the bowels may move sufficiently though reluctantly, with the gradual production of the secondary changes typical of the classical Hirschsprung's disease

Acute obstructive symptoms in this disease can be found at two stages of the condition , first, they may occur in the neonatal period or, second, at a later date when the clinical picture is more readily recognised In the latter, marked peristalsis and explosive borborygmi accompany an obstructive incident, and temporary relief may be obtained, if the narrow segment is short, by the passage of a rectal tube Definitive treatment can be instituted later by colostomy, and rectosigmoidectomy (Stephens, 1950) In the neonate, the diagnosis and treatment are not so easily defined The diagnosis is suggested by the inadequate passage of meconium, by increasing signs of low intestinal obstruction, by the small capacity of the rectum on digital examination and by X-ray investigation Hitherto, these cases have been diagnosed usually as some form of organic obstruction, and at operation the surgeon has been perturbed by his inability to display any cause of that nature However, in these cases it is possible to find a portion of the gut in which there is transition from the dilatation of obstruction to bowel of normal dimensions The typical agenesis of the intramural ganglia has been found to exist in the undilated portions of the gut, usually extending for considerable distances—to splenic flexure, proximal colon or even into the terminal ileum (Forshall, Rickham and Mossman, 1951) The only treatment of any avail is external diversion above the site of the neurogenic obstruction No neonate will tolerate a large exclusion of the colon, and far less so an ileostomy, even for a short time Therefore, in these extensively involved cases it seems improbable that any curative operation can be devised

Imperforate Anus—Four types of this condition are usually described The first includes all cases of stenosis, which may be of only minor extent and present no acute problems , or they may be of severe degree with small external and ectopic openings These cases may behave initially like complete imperforation but even the narrowest channel, exuding only an occasional bead of meconium may, by persistent and regular dilatation, be enlarged into an opening capable of functioning normally (Browne, 1951) In the second degree, a persistent cloacal membrane occludes a normal anal canal The perineal appearance makes this type readily recognisable Cruciform incision of the membrane provides relief, but a fibrous stricture will inevitably develop unless regular bouginage is performed in the ensuing months In the third degree, the rectum ends blindly at a considerably higher level, and not infrequently a fistulous communication with adjacent organs—bladder, urethra, or vagina—may exist It is for this type and especially for those cases with fistula, that more radical measures are now advocated Colostomy relieves the obstruction but renders any subsequent operation more difficult by fixation of the gut and by impairing later appreciation of a fistula The distance of the rectum from the perineum can be estimated by radiography If the distance is less than one inch, the blind end can be approached from below through the external sphincter muscle which is always present (Ladd and Gross, 1934) The pouch is often intimately fused with anterior structures, especially when fistulous communication co-exists If operation is undertaken before there is much distension of the pouch, its definition may be rendered difficult by recession upwards as dissection proceeds Because of these difficulties a combined abdomino-perineal operation is now being advocated (Rhodes, 1946 , Norris, Brophy and Brayton, 1949) From above, fistulæ are more clearly identified, and the pouch more easily and more completely mobilised Approximation of it to the perineum is thus affected with less risk of retraction through tension, and stricture is avoided The fourth type is the rarest and most dangerous for there is persistence of an occluding membrane within the anal canal or rectum Externally the anus appears normal, but the total failure to pass meconium should call for rectal examination Delay in recognition is frequent and obstruction is often present to a degree so marked that colostomy alone may be practicable

ALIMENTARY ANOMALIES WITH OBSTRUCTION AND FISTULA

As described above Type III imperforate anus is often accompanied by fistulous communications , similar dual lesions are sometimes found in the œsophagus and in relation to patency of the vitello-intestinal duct

Congenital Atresia of the Œsophagus with Tracheo-œsophageal Fistula —Various types of this anomaly occur, in the commonest of which the lower part of the œsophagus forms a fistulous communication with the respiratory tree in the trachea, at the carina, or with one of the main bronchi The condition should be suspected in any new-born infant who persistently accumulates oral secretions, which periodically cause attacks of choking, frothing at the mouth and cyanosis These symptoms are exaggerated by attempts to feed the child The careful passage of a firm and moderately large rubber catheter reveals an impediment to its progress into the stomach. This finding warrants immediate investigation. Only as much lipiodol as is necessary to outline the upper œsophageal pouch should be used, although a small spill over into the trachea can occasionally define the fistulous communication with the lower œsophagus. Sometimes it is preferable to confirm the presence of this and its level by bronchoscopy. A fistula can be confidently predicted on the radiographic appearance of air in the stomach.

At operation, general anæsthesia through an intra-tracheal tube is essential for the adequate maintenance of controlled respiration. In these infants the pleura is exceedingly thin and very easily "holed," either on the side of approach by the extrapleural route, or during mobilisation of the œsophageal segments on the contra-lateral side. The approach is by resection of the fourth rib on the right side. Where there is absence of gas in the stomach, indicative of atresia of the lower segment also, a left-sided approach may be used in order that œsophago-gastrostomy may be attempted if necessary—a formidable procedure at this age which has been successfully performed. Most surgeons (Bigger, 1949) advocate an extrapleural approach in order to limit any infective process which will follow a leak at the anastomosis—a not infrequent complication. That approach is time-consuming, and fails to achieve its object if the pleura is "holed." The transpleural approach is immediate and direct. Usually, the tracheal fistula is readily found on the posterior aspect of the lower trachea; but, if it is situated at the carina or in a bronchus, considerable difficulty may be encountered in defining the lower portion of the œsophagus. Mobilisation of the œsophagus should be limited in order to preserve its blood supply. The fistulous communication is divided and the tracheal end closed by ligature, which is safe if placed with care. The hypertrophied upper œsophageal pouch is found towards the thoracic inlet; a tube passed into it by the anæsthetist helps in its identification. A traction stitch placed in its fundus aids in the mobilisation on its deep aspect. An estimate of the practicability of anastomosis can now be made. Every millimetre of each structure is valuable; the avoidance of tension is most essential, and if the narrower lower segment can be invaginated into the wider upper pouch a firmer two-layer anastomosis is obtained. End-to-end junction may be all that is possible but the distal portion holds stitches poorly, and the risks of leaking are considerable. Fixation of the upper pouch to the prevertebral fascia with a view to taking tension off the suture line is inadvisable, for such fixation only submits it to greater stresses from respiratory excursions. Mediastinal and intrapleural drainage are wise precautions before closure of the chest. Depending upon the fears of the surgeon for his anastomosis, gastrostomy may be performed some hours later. In the most hopeful cases sterile feeds with antibiotics by mouth can be given after forty-eight hours. Post-operative difficulties are—leaking at the anastomosis and the formation of fistulæ, intrathoracic and mediastinal sepsis, all of which render gastrostomy essential In the later stages strictures may develop and require prolonged treatment by dilatation However, this anomaly, once consistently fatal, can now be corrected

ALIMENTARY OBSTRUCTIONS ASSOCIATED WITH HÆMORRHAGE

The discussion of emergency alimentary conditions concludes with mention of important lesions which combine obstructive and hæmorrhagic manifestations The acquired condition of acute intussusception is not uncommon, but the urgent states produced by Meckel's diverticulum or an associated peptic ulcer of the adjacent bowel, by heterotopic islets of gastric mucosa, and by duplications of the gut, are much less frequently seen

Acute Idiopathic Intussusception—The clinical picture of acute idiopathic intussusception is clear in the minds of most doctors However, the history, symptoms and signs are by no means always true to type The child does not always scream with spasmodic agony, it is often found to " girn " its discomfort into the pillow while wriggling on its hands and knees The quiet intervals accompanied by pallor occur more consistently Vomiting is not an early sign, but comes with increasing intestinal obstruction Blood with mucus may not appear from the rectum for at least twelve hours and in subacute and chronic cases, not infrequently found in the slightly older child, it may not appear at all

The clinical signs are also well established, but there are certain points worthy of emphasis The commonest site for the palpable tumour is in the right hypochrondrium Here it can be masked under the projecting liver of the infant, and all infants object to pressure on the liver The tumour is most easily palpated when it is hardest Then, during an attack of pain, the examination is more difficult A fleeting impression of the presence of a tumour in this region is sufficient to warrant operative measures When present in the left half of the abdomen there is never any difficulty in feeling the tumour Its bulk is larger and tension on the mesentery has drawn it towards the umbilicus The presence of the tumour in the rectum is by no means of serious prognostic import, rapid progression often results in relatively easy reduction Failure to advance often implies early tension on the mesentery This is an important factor in the production of the changes which lead to irreducibility The Signe de Dance of " palpable emptiness " in the right iliac fossa is most unreliable When the tumour is proximal to the splenic flexure rectal examination may not reveal any blood or mucus, but simultaneous abdominal palpation along the line of the colon from the suspected tumour towards the rectum may reveal this latent sign Unless the surgeon is an exponent of the hydrostatic method of reduction of intussusception, barium enema investigation is seldom necessary This method of treatment is eminently successful in the hands of many surgeons, but direct surgical measures are ultimately safer, and cannot ever be entirely avoided

Intussusception is an intestinal strangulation and if much blood has been lost it should be replaced When the reduction is difficult gentle dilatation at the neck of the tumour with the little finger, and gentle traction upon the entering loop are as much as is permissible No longer than five minutes should be given to attempts at the reduction of a stubborn tumour, and no other operative procedures to encourage reduction should be done Most tumours will reveal their irreducibility before this lapse of time Resection and end-to-end anastomosis do not now have a high mortality and experience has shown that it is often in the interests of the child to proceed to resection, even although persistent and prolonged manipulation might in the end achieve reduction There is no certainty that the intussuscepted area will then be found viable, and even if it is so, the post-operative course of these children is often complicated, and a fatal outcome is not unusual It is possible that this may be due to the absorption of katabolic products, analogous to those found in the " crush syndrome "

In the face of irreducibility there is no doubt that resection is the procedure of choice It is at once curative and final In the very ill child, exclusion, exteriorisation, or even ileostomy have been performed Although successes have been achieved by these means, early resection in the case of exclusion, and early reconstitution of the bowel in exteriorisation and ileostomy are essential But these are major procedures which throw an additional strain upon an already weakened child The frequent finding of undue mobility of the cæcum and ascending colon renders resection relatively easy and an aseptic two-layer anastomosis does not take long Therefore, resection is recommended with confidence

Meckel's diverticulum —Persistence of vitello-intestinal ductal tissue—more often called Meckel's diverticulum—is the commonest of the anomalies of the gastro-intestinal tract Complete patency of the duct at the umbilicus is seldom urgent unless atresia of the ileum exists below Closure, but with persistence of intestinal mucosa at the umbilicus, produces a " mulberry tumour " (enteroteratoma), the history of which in earlier life is a useful pointer to a Meckel's diverticulum in any patient with acute abdominal symptoms in later life Such a diverticulum may never cause symptoms, but if it has attachment to the anterior abdominal wall at the umbilicus, the risk of intestinal volvulus is ever-present and may arise at any age, though it is relatively infrequent in infancy , also, hæmorrhage from ulceration of the intestinal mucosa adjacent to the diverticulum may occur at any age but, relatively, this is quite often encountered in the infant This ulceration is produced by the secretion of islets of gastric mucosa within the diverticulum Such islets may occur in other sites of the bowel with the production of similar vague symptoms of recurring abdominal pain, sometimes related to the taking of food The urgent symptom, however, is rectal bleeding which, usually preceded by minor incidents, is often profuse and can be exsanguinating Resection of the affected segment and the diverticulum is indicated It is doubtful whether acute Meckel's diverticulitis ever occurs as a bacterial process such cases are almost certainly due to ulcer and the associated reactionary changes Perforation is a rare complication of the clinical picture , adhesion and obstruction are more common A freely mobile diverticulum can tie itself into the most intricate knots, often ensnaring bowel loops in the tangle Such obstructions, complicated by strangulation, are straightforward in their diagnosis and treatment

Intestinal Duplication —Duplication of portions of the alimentary tract is probably the rarest anomaly of this system It arises from a double recanalisation of the intestinal tract after the solid stage of the sixth and seventh embryonic weeks Duplications are an inherent part of the intestinal tract and occur most often in the ileum The duplicated portion may be very short , less often it extends over a considerable length of the gut Symptoms are caused by those which are closed completely off from the normal bowel Lined with normal mucosa, a cyst is formed by gradual distension with secretions Although true mesenteric cysts do occur, there is no doubt that in the past duplications have been mistaken for these The distinction is important, for a cyst can often be enucleated, but the muscular wall of a duplication is intimately fused with the associated normal gut and removal cannot be accomplished without damage to that structure and its blood supply Resection of the abnormal portion is essential Symptoms are caused, either by increase in size interfering with the blood supply to the main tract, or occluding the lumen of the normal tract In the first instance, extravasation of blood occurs into the intestinal tract Warning bleedings may occur, but the hæmorrhage may be considerable Obstructive symptoms from occlusion are of an increasing nature The two pictures are not infrequently combined, one predominating over the other It is usual for a duplication to cause trouble relatively early in life, and on examination a mobile and possibly spherical tumour may be felt within the abdomen Within the thorax, in the pelvis, and when related to the stomach, the symptoms are due to the effects of pressure upon the neighbouring organs Excision may be less urgently required, though inevitably essential

INFECTIVE CONDITIONS

Umbilical Sepsis —In the neonate sepsis at the umbilicus is less frequently encountered than previously, but the dangers of peritonitis, liver abscess, and septicæmia still exist, although their control is now more effectively obtained A distant and crippling complication of this same focus of infection is arthritis of a major joint, usually at the hip Early recognition, when the damage could be limited, is not easy , for, in common with other acute infective processes in early life, the general body response is weak and undemonstrative

Osteomyelitis.—In the infant, osteomyelitis of the classical type is unusual, but infection is not infrequently encountered in the jaws, and especially in the maxilla. The infection is thought to arise in the tooth follicles. Extension upwards to the orbit sometimes produces alarming displacement of the ocular globe itself, and evacuation of such an abscess may be urgently required.

Acute Appendicitis.—In childhood, acute appendicitis is a common disease. In infancy, although it is not unknown at quite an early age, it is generally seldom encountered under the age of two years. Delays in the diagnosis are common, and peritonitis is frequent. The treatment at all stages of the disease is operative, and it is a matter of recurring interest how smooth and uncomplicated is the usual post-operative course of the very young. More often it is an older child and a male who succumbs to the complications of toxæmia, paralytic ileus or organic intestinal obstruction.

URO-GENITAL CONDITIONS

In infancy, emergency conditions of the urogenital system are few. *Injuries* are seldom sustained at this age, but it is important to remember that the infant's bladder, even when empty is an intra-abdominal organ. Damage to the kidneys or ureters, which are surrounded by little fat and covered by a tenuous peritoneum, may be associated with peritoneal contamination. *Renal infarction* of a type peculiar to the very young is a condition for which urgent treatment may be necessary. Considerable dehydration may permit spontaneous thrombosis of one or both renal veins, and massive venous infarction may arise in the course of a severe pyelonephritis. Blood and pus appear in the urine and the enlarged organ or organs are easily palpable. For unilateral involvement, nephrectomy can be curative. As parenteral pyelography at this age is not always satisfactory, at operation, proof of the second and adequate kidney is obtained by direct palpation of it across the peritoneal cavity.

Perhaps *meatal ulcer* is not a true surgical emergency, but it is certainly a social one. In the circumcised child this simple condition can produce the most acute pain and with the associated ammoniacal dermatitis of the napkin area causes marked irritability. At night, these manifestations are always most severe. The remedy for the distressed child and his parents is simple (Hamilton and Middleton, 1927). Impregnation of all napkins with a saturated solution of boracic acid prevents the bacteriological splitting of urea and the formation of ammonia. *Paraphimosis* seldom arises in the infant unless from the ill-advised and unnecessary retraction of the prepuce. Each baby boy is born with an irretractable prepuce, which if left entirely alone will enlarge adequately at its orifice. Retraction only opens up prematurely the preputial sac in which infection may thereafter occur and small tears in the prepuce itself are caused and lead to scarring and phimosis. True congenital phimosis is rare, and with this and ritual the only criteria for circumcision are—fibrotic phimosis, recurrent balanitis and paraphimosis

FOREIGN BODIES

Of foreign bodies in the natural passages of the body little needs to be said In the alimentary tract it is important not to rely only on a film of the abdomen for the revelation of a swallowed metal object, a neck and chest film is of even greater importance It is impaction in the pharynx or œsophagus, and entrance of the foreign body into the respiratory tree that are of urgent significance, and urgent symptoms are not always evident in these circumstances A negative abdominal film alone may mislead dangerously In the stomach or intestine early surgical removal is indicated for objects over two and a half inches in length, especially for those that are sharp-pointed Operative removal is required of any object retained in the stomach for three weeks, or delayed in passing on in the duodenum or lower reaches of the gut for more than three days

CONCLUSION

That this work amongst infants is rewarding will be appreciated especially by those whose chief concern is with the adult and the ageing, in whom the problem is often that of disease and the degeneration of an unresponsive body The latent attributes of an infant rescued by surgery are relatively unlimited and certainly unknown The presence of these children as they grow in stature and develop in mind is a recurrent joy and stimulus therefore, in this world of lowered values, even ethical and moral, I ask in all humility—Is the saying not still true ?—

> " He stands the straightest who stoops to help a child "

REFERENCES

BIGGER, I A (1949), *Ann Surg*, 129, 572
BROWNE, D (1951), *Ann Roy Coll Surg*, 8, 173
FARBER, S (1933), *Journ Amer Med Assoc*, 100, 1753
FORSHALL, I, RICKHAM, P P, and MOSSMAN, D B (1951), *Arch Dis Childh*, 26, 294
GLOVER, D M, and BARRY, F McA (1949), *Ann Surg*, 130, 480
GROSS, R E (1948), *Surg*, 24, 277
GROSS, R E, and BLODGETT, J B (1940), *Surg Gynec Obstet*, 71, 520
HAMILTON, A J C, and MIDDLETON, D S (1927), *Lancet*, 2, 639
HIATT, R B, and WILSON, P E (1948), *Surg Gynec Obstet*, 87, 317
LADD, W E (1933), *Journ Amer Med Assoc*, 101, 1453
LADD, W E, and GROSS, R E (1934), *Amer Journ Surg*, 23, 167
NORRIS, W J, BROPHY, T W, and BRAYTON, D (1949), *Surg Gynec Obstet*, 88, 623
RHODES, R L (1946), *Ann Surg*, 123, 877
STEPHENS, F D (1950), *Ann Roy Coll Surg*, 7, 257
SWENSON, O, RHEINLANDER, H F, and DIAMOND, I (1949), *New England Journ Med*, 241, 551

OBSERVATIONS ON THE ÆTIOLOGY OF BRONCHIECTASIS

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A STUDY of the literature of bronchiectasis shows that the majority of surveys have been conducted either on the selected material which finds its way to the large hospitals or on groups of individuals, nearly all male, who have been singled out for military service It is also apparent that certain of its aspects have received greater attention than others For this reason I have conducted an inquiry into the ætiological factors of bronchiectasis over an area in Bedfordshire where a survey can be arranged to cover most cases of the disease, both those already proven and those requiring diagnosis This area is sufficiently far from a large centre for the local hospital to be the natural place of reference, but not so remote as to preclude reasonable facilities for investigation Any inquiry into the ætiology of such a chronic condition, in which a long interval usually passes between the onset of symptoms and the date of diagnosis, offers special difficulties in obtaining an accurate history, particularly if one is dependent on the memory of the patient or that of an older relative for past events The many acute diseases of infancy and childhood, which are apt to follow each other very quickly, also render it hard or impossible sometimes to decide which was responsible for the damage to the bronchi Great care has been taken to secure as exact a history as possible, a number of old medical records both of hospitals and general practitioners have been of much help in this direction The following brief case report illustrates how unreliable the information given by a patient or his relations may be

A boy aged 10 was referred in 1949 because of persistent cough following a cold A radiograph showed slightly increased pulmonary markings in the right middle zone with questionable hilar calcification Pertussis followed by cough for about nine months was the only relevant illness reported during his previous history Later a radiograph taken in 1944 and the results of investigations at another hospital became available They proved conclusively that he had suffered from primary tuberculosis and that successive films had shown only partial clearing of the lesion A bronchogram (Fig 1) in 1951 confirmed the presence of bronchiectasis which might with justice have been attributed to pertussis

In this series no case of bronchiectasis occurring in the course of a disease of more consequence to the patient than the dilatation itself has been included—thus no bronchiectasis associated with conditions such as carcinoma of the bronchus or the adult form of pulmonary tuberculosis A review of the ætiological factors concerned is necessary before considering the results obtained in this investigation

Pneumonia and the Specific Fevers—The commonest antecedent illness from which date a history of symptoms can be obtained is "pneumonia" It has been taught that broncho-pneumonia or lobular pneumonia is more frequent in children than lobar pneumonia, and hence as symptoms most often begin in childhood broncho-pneumonia has been considered the condition from which bronchiectasis most usually develops However, since radiography has been applied more extensively to respiratory disease, it has become known that non-tuberculous consolidations of lobar extent are not uncommon in children, and that they may pass on to bronchiectasis Furthermore, collapse of a lobe or lung produces an illness often not differentiated from a true pneumonia, and acute illness diagnosed as pleurisy may well be accompanied by underlying consolidation These facts make it obvious that an exact division of patients into those whose disease was preceded by broncho-pneumonia, lobar pneumonia or collapse must be very difficult, and in this paper "pneumonia" will be used without further qualification to describe any respiratory illness, the symptoms of which were consistent with the diagnosis of any of the above conditions

The relationship of pertussis and measles in children and influenza in adults to bronchiectasis is also well known, and adds a further complication—whether these infections of themselves are followed by bronchial dilatation, or whether they merely pave the way for further bacterial invasion and encourage infected collapse due to aspiration Ramsay and Scadding (1939) drew attention to the fact that such pneumonias may be accompanied by little in the way of symptoms or abnormal physical signs With regard more particularly to measles, Kohn and Koiransky (1929) in a series of 130 children demonstrated pneumonia radiologically in 62 4 per cent under the age of four and in 42 2 per cent over this age, and often in the absence of signs suggestive of pneumonia Measles, however, is not a very frequent precursor of bronchiectasis Pertussis, on the other hand, is regarded as a common cause of the condition (Lander, 1950) Nicholson (1949) observed 44 children, who were sufficiently ill to be admitted to hospital with pertussis, for periods up to one year or until the radiological picture returned to normal Seven children (15 9 per cent) suffered from collapse which was still present after one year, and hence probably had developed bronchiectasis

Chronic Respiratory Catarrh—The first respiratory symptoms complained of in a considerable number of patients consist of recurrent bronchitis or "chestiness" since infancy. Very little is known about the ætiology of these cases, but it is doubtful if uncomplicated chronic bronchitis leads to bronchial dilatation Diamond and Van Loon (1942) did not note that chronic bronchitis in children developed into bronchiectasis although the symptoms of the two diseases were much alike Most writers have mentioned these factors but with scant comment An exception must be made in the case of those authors who have judged allergy to be an important antecedent influence in

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bronchiectasis It may be remarked that in the same way as pneumonia is difficult to diagnose, so is uncomplicated bronchitis, and it is a common-place for a clinical diagnosis of bronchitis to be associated with radiographic shadows suggestive of pneumonia

Primary Tuberculosis—It has been known that an enlarged tuberculous lymph gland could compress a bronchus and lead to pulmonary collapse since Gairdner described the association in 1850 at autopsy The conception that bronchial dilatation might follow as a sequel is of relatively recent development although two such cases were reported by Gee in 1877 Brock, Cann and Dickinson (1937) gave particulars of bronchiectasis following obstruction of a bronchus by tuberculous adenitis in several children They stated that " No proven cases observed in childhood have been followed into adolescence or adult life, and the development of true bronchiectasis demonstrated clinically and radiographically " Since this time series have been set forth by Kent (1942), Richards (1944), Graham and Hutchison (1947), Roberts and Blair (1950) and others, drawing attention to this sequel of the primary complex

Mustard Gas—Ever since the 1914-18 World War a proportion of men who were exposed to inhalations of mustard or other vesicant gas, have complained of " bronchitis " and chronic cough Loeper (1919) studied a number of gassed patients at autopsy and found bronchial dilatation present, and Bonnamour, Badolle and Gaillard (1929) confirmed these findings in survivors by means of bronchography Carr, Denman and Skinner (1947) investigated a number of workers who had been exposed to similar fumes by accident during the recent war, bronchograms were done in 144 and bronchiectasis found in 87

Post-Operative Pulmonary Complications—In 1908 Pasteur drew attention to massive collapse following abdominal operations, but Elliott and Dingley (1914) were the first to suggest that such collapse might be caused by blockage of the bronchi due to retained secretions At the present time it is generally believed that retention of secretion acts as the primary factor and that any condition which makes clearing of the air passages difficult, renders atelectasis more likely If the collapse is persistent infection may occur as a complication and bronchiectasis follow Bronchiectasis following tonsillectomy is probably due to the inhalation of septic material

Pulmonary Sequelæ of Irradiation—The literature on intensive irradiation of the thorax often mentions fibrosis of the lung as a sequel, but I have been unable to find any reference to bronchiectasis, although it accompanies pulmonary fibrosis associated with other conditions Huguenin, Lemoine and Fauvet (1947) described a patient who died with symptoms suggesting an infected bronchiectasis following post-radiation pulmonary disease, but unfortunately no post-mortem material was obtained One case occurred in the present series

Pulmonary Infiltrations and Eosinophilia—A chronic type of pulmonary infiltration associated with eosinophilia, and closely related to asthma, was described by Harkavy in 1941 Livingstone (1950) has described the association of these infiltrations with bronchiectasis, usually patchy in distribution and fuso-saccular in form

Apart from the more obvious causes of bronchiectasis there are certain more general and less clearly related factors which must be considered as having possible significance

Bacteriology—Thorpe (1929) recorded a mixed bacterial flora from 27 specimens of sputum obtained direct at bronchoscopy, and Greey (1932) in 9 lobectomy specimens examined under sterile conditions confirmed these findings Smith (1927 and 1930), however, found spirochetes and fusiform organisms in the sputum of 49 out of 60 cases of bronchiectasis He considered that they initiated the disease by destroying the elastic and muscular tissue of the bronchus Smith and Rusk (1927) on the contrary expressed the opinion of most observers that spirochetes and fusiform bacilli are not primary invaders, but represent secondary infection Allison, Gordon and Zinnemann (1943) thought that the hæmophilus influenzæ played an important rôle in bronchiectasis as it was present in the sputum of 65 of the 100 cases which they investigated Very numerous examinations of the bacterial flora of sputum in patients suffering from bronchiectasis have been made, but the consensus of opinion does not attribute the disease to any specific infective agent

Sinusitis—Sinusitis has been known to be frequently associated with bronchiectasis since Thomson (1914) noted its presence with purulent bronchorrhœa, but agreement has not been reached regarding its significance It has been proved without doubt that material can be aspirated from the nasal passages into the lungs, and that the aspiration of pus into the bronchi from infected sinuses is extremely probable, but there is no unequivocal evidence that bronchiectasis is caused by the inhalation of septic material from the nares Clinically, it is known that sinusitis is a very common accompaniment of bronchitis and other acute infections of the respiratory system, as well as bronchiectasis Walsh and Meyer (1938) investigated 217 patients, excluding cases which had followed the inhalation of a foreign body and also congenital bronchiectasis They found 145 (66 8 per cent) with evidence of sinusitis These findings and many others show that those with bronchiectasis have a high incidence of sinusitis, but it should be remembered that chronic sinusitis is far commoner than bronchiectasis, and that the latter is not seen to develop at all frequently in patients suffering from sinusitis Nor is there any sound evidence to suggest that infection often spreads from the bronchi upwards to the sinuses, although purulent sputum can certainly be coughed into them , an observation easily confirmed by the presence of iodised oil within the sinuses after bronchography

Allergy—Cases of massive atelectasis occurring with asthma have been reported by Kamchorn and Ellis (1921) and Kessel and Hyman (1928), and in children by Peshkin and Fineman (1931) Miller, Piness, Feingold and Friedman (1935) and others have drawn attention to the relatively common occurrence of respiratory disturbances, which they thought were allergic in origin and not due to infection, in bronchial asthma They described shadows, both segmental and lobular in distribution, which commonly cleared after the disappearance of the allergic state, but might recur in the same or a different position with a further attack of allergy There is no doubt that asthmatics are sometimes labelled as suffering from pneumonia or recurrent pneumonia and even pulmonary tuberculosis when the radiological abnormality is primarily due to allergy Tucker (1931) showed the way in which lobar collapse occurs in asthma by removing the obstructing plug of secretion through a bronchoscope, after which re-expansion took place The above work has shown that atelectasis can occur and recur in asthma and allergic bronchitis, but has in no way proved that there is any ætiological significance between this disease and bronchiectasis A definite association between the two conditions is frequently met, but both are common The majority of authorities have not thought that asthma occurred especially in bronchiectasis Diamond and Van Loon (1942) found only 4 per cent of their bronchiectatics with asthma whereas it was present in 17 3 per cent of their chronic bronchitics Waldbott, Kaufman and Merkle (1950) found only four cases of permanent bronchiectasis among 756 patients with chronic asthma, although in nine others they found evidence of reversible bronchiectasis

Asthma, however, is not the only condition judged to be allergic and criteria have varied considerably as to what may be considered so Watson and Kibler (1938) believed that 90 per cent of bronchiectasis seen in their area was allergic in origin They thought that the first stage was " basal allergic bronchitis " which, if untreated, developed into bronchiectasis In their opinion the allergic swelling of the mucosa and the outpouring of secretion caused collapse The presence and permanence of bacterial infection determined whether or not bronchiectasis developed Essentially similar findings were reported by Davison (1944) who judged 80 per cent of 50 bronchiectatics to be allergic He considered that hypersensitive children who suffered from an acute respiratory infection were more likely to be left with bronchiectasis and sinusitis His criteria of allergy were the presence of nasal polyps or many eosinophils in the nasal or bronchial exudate Thomas, Van Ordstrand and Tomlinson (1945) noted a major allergic respiratory condition in nearly half of 190 consecutive bronchiectatics

These figures for allergy in bronchiectasis are very suggestive but are subject to the same criticisms as those for sinusitis and bronchiectasis Bronchiectasis is seldom seen to develop in the asthmatic or allergic patient—the association is noticed after the development of ectasis However, it is likely that this factor has been paid too little attention in the past, and the considerable number of bronchiectatics whose only past abnormality has apparently been chronic respiratory catarrh must be observed Such symptoms are suggestive of allergy, and the work of Diamond and Van Loon (1942) must be considered in relation to the fact that in 37 per cent of their 75 bronchiectatics no obvious causal factor was found It seems certain that much further work must be done upon this group of " chesty " children and also on the considerable group of adults who trace their symptoms to an attack of bronchitis before the factor of allergy can be discounted, but no one has shown by prolonged observation that more of those who suffer from asthma or allergic bronchitis are liable to develop bronchiectasis than the remainder of the population

Congenital Bronchiectasis—There has been much discussion but no agreement as to the reality of congenital bronchiectasis It was described as occurring in as many as 10 per cent of 200 cases by Whitwell (1949), Lander (1947) takes the opposite view that this condition does not exist I have not been able to find any pathological description of congenital bronchiectasis in which the bronchi communicated with the cystic spaces in a foetus which had never breathed, thus undoubtedly proving that the dilatations were not acquired For these reasons and also because in those cases in this series, which were accompanied by thin-walled " cystic " dilatations and could be placed in this group, a less dubious ætiological factor was present, attention has not been directed to this cause

MATERIAL AND CRITERIA OF DIAGNOSIS

This survey was conducted over a period of five years (1947-1951) from a chest clinic responsible for a population of about 150,000 centred on Bedford, a county town and urban district of over 60,000 inhabitants which is surrounded by small urban and rural communities The majority of patients were referred for diagnosis or found in the course of routine radiography, but 21 adults and 5 children were sent up for observation or treatment with the diagnosis already known One hundred and thirty-seven adults (73 male and 64 female) and 29 children (14 male and 15 female) were collected in whom the dilatation was proved by bronchography All ages have been calculated from the time of first coming under my care, and those under the age of 15 have been classified as children A further 48 cases of undoubted bronchiectasis were seen, but as they were not subjected to bronchogram they have been ignored in the detailed analysis As stated already, bronchiectasis that has followed or accompanied a disease which is of more importance to the patient than the dilatation of the bronchial tubes themselves has not been included, and so no case caused by inhaled foreign bodies, carcinoma of the bronchus, metastatic carcinoma, aneurysm and diseases of such a nature Post-primary tuberculosis has been most carefully excluded as an ætiological factor. The primary complex of tuberculosis causing pulmonary collapse followed by bronchiectasis has been admitted because it is felt that the dilatation is more important to the patient than the old healed lesion and also because of the known impossibility of exclusion in a small number.

In the past criteria of diagnosis have varied very considerably For instance, Farrell (1936) diagnosed bronchiectasis on the plain

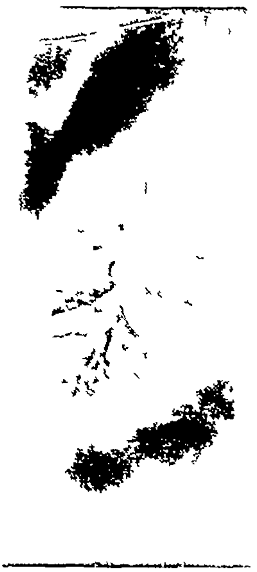

FIG 1 —Right lateral bronchogram on 5 1 51 showing bronchiectasis of the apical segment of the right lower lobe

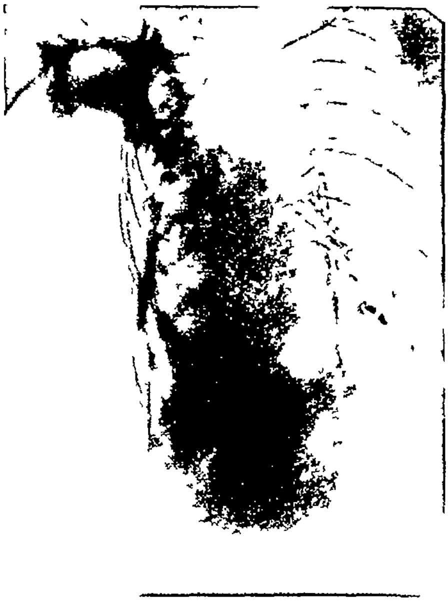

FIG 2 —Antero posterior bronchogram on 4 4 51 showing total bronchiectasis of the right lung and dilatation of the basal branches of the left lower lobe

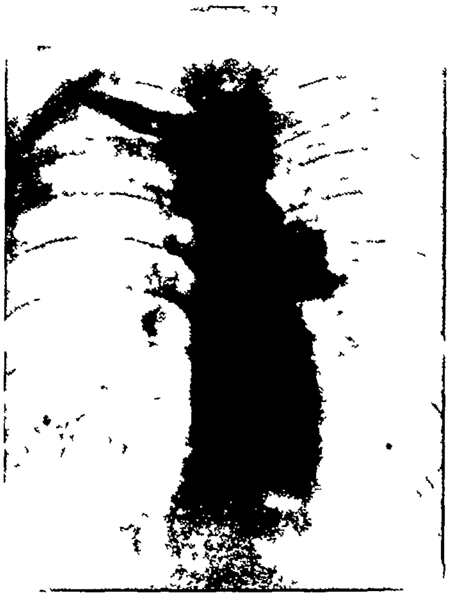

FIG 3 —Postero anterior radiograph on 22 4 49 showing opacities in the right upper and middle zones and increased shadows spreading upwards and outwards from the left hilum

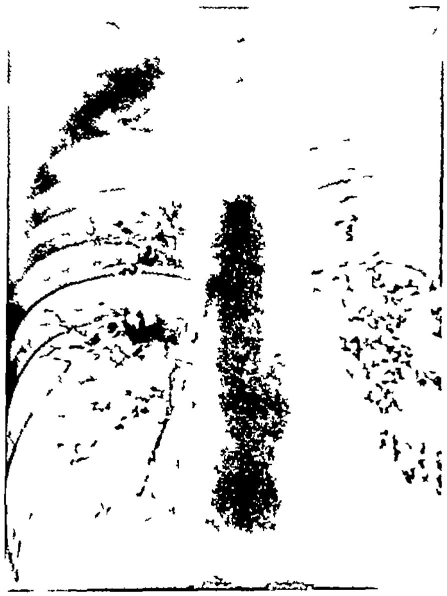

FIG 4 —Antero posterior bronchogram on 30 8 50 showing bilateral bronchiectasis of fuso saccular type

radiograph even if iodized oil showed no dilatation, and others have done similarly whenever the alveoli failed to fill with oil Bradshaw, Putney and Clerf (1941), Thomas *et al* (1945) and others have been satisfied with the evidence obtained on bronchoscopic examination Only a few authors, among whom Ogilvie (1941), Evans and Galinsky (1944) and Waldbott *et al* (1950) may be mentioned, have drawn attention to any difficulty in interpreting dilatation on bronchograms In the present investigation some uncertainty in deciding whether true dilatation was present has been experienced in a small proportion

TABLE I

Cases of Bronchiectasis in Adults and Children Analysed According to Primary Ætiological Factors

Ætiological Factor	Adults		Children		Adults and Children	
	No	Per cent	No	Per cent	No	Per cent
Pneumonia	64	46 7	2	6 9	66	39 8
Pneumonia and empyema	5	3 7			5	3 0
Pertussis	8	5 9	5	17 2	13	7 9
Pertussis and pneumonia	3	2 2	2	6 9	5	3 0
Pertussis and measles	1	0 7			1	0 6
Influenza	4	2 9			4	2 4
Measles	1	0 7			1	0 6
Measles and pneumonia	1	0 7	2	6 9	3	1 8
Diphtheria	1	0 7			1	0 6
Scarlet fever with pneumonia	1	0 7			1	0 6
" Black Fever "	1	0 7			1	0 6
Bronchitis	13	9 6	5	17 2	18	10 9
Cough since infancy	12	8 8	5	17 2	17	10 0
Primary tuberculosis	5	3 7	7	24 2	12	7 3
Mustard gas	8	5 9			8	4 9
Post operative chest complications	4	2 9			4	2 4
X radiation to chest	1	0 7			1	0 6
Pulmonary infiltrations with eosinophilia	1	0 7			1	0 6
Pulmonary abscess	1	0 7			1	0 6
Hæmorrhagic disease of the new born			1	3 5	1	0 6
Unknown	2	1 4			2	1 2
Total	137	100 0	29	100 0	166	100 0

No bronchi that have tapered towards the periphery nor any that were partially filled unless grossly dilated have been judged ectatic A number of border-line cases have been omitted, and those included have been viewed by two or more observers all of whom have diagnosed bronchial dilatation independently

ANALYSIS OF ÆTIOLOGICAL FACTORS IN THIS SERIES

The primary ætiological factors found in this survey of 166 patients are presented in detail in Table I Whenever such factors have been complicated by a second disease this has been noted under a separate heading and percentages have been estimated individually These calculations have been made for adults, children, and the two combined, so that they may be compared with those found elsewhere in various age groups It must be stressed that although many writers have published figures on the ætiology of bronchiectasis, there is no uniformity in their methods of presentation, and some articles do not state the age groups of those described There are also large differences in the percentage of cases reported as of unknown ætiology A further source of error lies in the fact that some series include a small proportion of bronchiectasis following the inhalation of foreign bodies and carcinoma of the bronchus

Pneumonia —The group of conditions combined under this heading has been found to be the commonest antecedent factor by the majority of investigators As noted previously it includes pneumonia, bronchopneumonia, pleurisy, empyema and severe respiratory illness The percentage due to pneumonia in the children (6 9 per cent) is a small one, conversely the percentage found in adults (50 4 per cent) and the two combined (42 8 per cent) is high

Pertussis —This factor has been mentioned in some series merely as pertussis and in others complicating diseases such as pneumonia or measles have been tabulated in addition There is a wide variation in these figures The position occupied by the present series is about the mean, and was 24 1 per cent among the children, 8 8 per cent among the adults and 11 5 per cent over the two combined

Influenza —This often diagnosed disease has been very variously treated as an ætiological factor , a number of authors have omitted it altogether In the adults and children combined it was the cause in 2 4 per cent , but it did not appear as a cause among the children It is possible that these cases might have been better placed under the heading of pneumonia

Infectious Diseases of Childhood —Measles, diphtheria, scarlet fever and other similar illnesses (excluding pertussis) have been considered under this heading As ætiological factors they have been described in very varying percentages In this series measles was judged responsible for 6 9 per cent of the children , diphtheria, scarlet fever and " black fever " for 3 5 per cent of the adults

Chronic Respiratory Catarrh —Recurrent or chronic bronchitis and cough since infancy have been mentioned as factors by some authors and probably by others have been considered as indefinite or unknown For example, Walsh and Meyer (1938) classed 47 per cent of their cases as of unknown ætiology and do not mention bronchitis at all, and in children Diamond and Van Loon (1942) placed 37 3 per cent in a similar category Here they have been divided into two groups —those who have had cough since infancy, and those who have traced their symptoms from recurrent or chronic bronchitis and " chest colds " The percentages found are high and are explained by the fact that whenever this complaint has been reported it has been treated as an ætiological factor and not classed as of unknown ætiology The two conditions together were responsible for 34 4 per cent of the children, 18 4 per cent of the adults, and 20 9 per cent of the whole number

Primary Tuberculosis—This was judged to be the cause in 7 (24 2 per cent) of the children, and 5 (3 7 per cent) of the adults, thus making a total of 12 (7 3 per cent) of the whole number Five of the children were seen at the time of the initial primary lesion, and the process watched from collapse to partial radiological clearing It is of great interest to note that three of them were left with radiological abnormalities that were in no way typical of healed primary tuberculosis The other 7 patients had heavy hilar calcifications associated with calcifications of segmental distribution extending into the lung of the typical type left behind by primary tuberculosis

Mustard Gas—Gassing was the ætiological factor in 8 (5 9 per cent) of the adults Every one of these patients had been in sufficient contact with mustard gas to need medical treatment, 6 had required admission to hospital None had complained of any symptoms referable to the chest previously, and all had suffered from cough and sputum gradually increasing in severity from the time of exposure

Other Causes—Injury to the lung following therapeutic irradiation of the chest is believed to have been the ætiological factor responsible for bronchiectasis in one woman It has not been possible to find a description of proved bronchiectasis following this cause, and therefore a short history of the case is given

CASE REPORT 10657—A married woman aged 39 had her right breast removed for carcinoma in May 1948 Before this she had suffered from no serious illness nor had she had any symptoms referable to her lungs A radiograph on 10th June 1948 showed no abnormality in the lung fields She was irradiated daily from 10th June to 16th June 1948 The skin dosage was 2814 R and the tumour dosage 2500 R applied to the chest wall and axilla Cough and sputum developed after this treatment, and a radiograph taken on 21st August 1948 showed bilateral abnormal shadows suggesting irradiation pulmonary disease A further film on 5th November 1948 showed considerable extension of the shadows on the right side with shift of the heart to the right, and slight diminution in the shadows on the left side Spontaneous fractures had also occurred in the 7th and 10th right ribs By July 1949 the patient was in very poor health with œdema of the ankles, free fluid in the abdomen and an enlarged liver, she was thought to have developed secondary deposits However, during the next six months she improved, all evidence of œdema disappeared and her complaints were limited to cough, sputum and general asthenia First seen on 5th January 1950 she was very thin, and the right hemithorax was much reduced in size, deeply pigmented anteriorly and presented physical signs typical of total collapse There was clubbing of the fingers, but no evidence of secondary deposits was found A radiograph taken on 13th January 1950 showed atelectasis of the right lung, and some thickening and crowding of the pulmonary markings over the lower zone of the left lung The heart was displaced to the right and an ununited fracture of the 7th right rib was present Her erythrocyte sedimentation rate was 68 mm at one hour (Westergren) and the sputum was negative for tubercle bacilli A bronchogram performed on 4th April 1950 showed bilateral bronchiectasis (Fig 2) Her condition remained little changed until April 1951 when she died suddenly, still with no evidence of secondary deposits

Recurrent pulmonary infiltrations with eosinophilia were present in one patient associated with bronchial dilatation As few cases of this syndrome have been described brief details are appended

Case Report 10659—A male aged 30 was first seen on 9th January 1950 during an acute respiratory illness The patient gave a history of asthma, frequent in childhood, but much less so of recent years For some years he had had bronchitis at intervals of a few months with normal health and no chest symptoms in between A radiograph on 12th January 1950 showed a small area of shadowing in the right upper zone and a few " ring " shadows in the middle zone, and extensive shadowing in the left upper and middle zones with numerous " ring " shadows The general picture suggested *pulmonary tuberculosis or possibly pneumonia The sputum was repeatedly* negative for tubercle bacilli, but unfortunately no blood count was done Shortly afterwards two previous X-ray films became available, the first of which had been taken in August 1948 and disclosed opacities of indefinite shape over both upper and middle zones, the second taken in April 1949 (Fig 3) showed a similar type of shadowing though of different distribution After viewing these radiographs it became obvious that an unusual condition was present, and serial radiographs showed that the shadowing on the left side was diminishing but that new shadows were appearing on the right side By June 1950 there was a small area of infiltration on the right side with a few " ring " shadows in the middle zone and on the left there were much more marked " ring " shadows in the upper and middle zones with a little irregular infiltration On 14th September 1950 he reported again having had an attack of asthma about 14 days previously The X-ray film was little changed, but a white cell count showed 9000 leucocytes per c mm, 14 per cent being eosinophils A bronchogram on 30th September 1950 (Fig 4) revealed bilateral bronchiectasis

Pulmonary abscess has figured in most series as an ætiological factor It may be difficult to tell whether this is a primary condition causing bronchiectasis or whether it arises secondary to long-standing disease In my series only one patient was judged as having developed bronchiectasis in the area occupied by a pulmonary abscess which was known to have arisen in a previously normal lung One other case came under observation for a pulmonary abscess, but this was thought to be a complication as it occurred in the only normal segment of a bronchiectatic lung in a patient with a long history of symptoms One child had suffered from hæmorrhagic disease of the newborn, and was believed to have inhaled vomited blood, he had coughed since infancy In two patients no ætiological factor could be discovered, one was referred because of dyspnœa on exertion, and one, a Pole, was unable to give any lucid account of himself

Associated Diseases—Sinusitis was present in 48 2 per cent of the children, in 28 4 per cent of the adults, and in 31 9 per cent of the combined groups In the main only patients who had suggestive symptoms or signs of sinusitis were investigated for its presence, and doubtless this accounts for the low overall percentage found The figure for children reflects the fact that the majority were sent to the special department for opinion, but also a far higher proportion had

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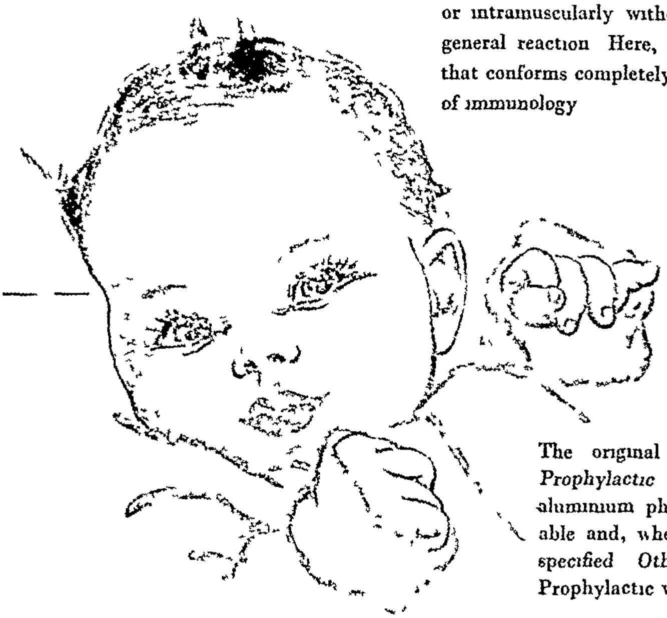

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symptoms referable to the area Asthma was present in 5 4 per cent. of the total

CORRELATION OF ÆTIOLOGICAL FACTORS AND OTHER ASPECTS

Age of Onset—Most authorities have found that about half their patients dated the onset of symptoms to the first decade of life, and in this series 73 out of the 154 with symptoms fell into this group When the ætiological factors are analysed this is seen to be largely dependent on the fact that many of the illnesses concerned are only common under the age of 10 Pertussis, the infectious fevers, and cough since infancy are obvious examples, and primary tuberculosis seldom gives rise to lymphadenopathy sufficient to cause bronchial obstruction except in children In every decade pneumonia proved to be the most frequent cause. In the first decade it accounted for 31 2 per cent, and by the third decade pneumonia and recurrent bronchitis were the only two factors of consequence remaining In spite of the early age of onset of symptoms the largest number (42 or 25 3 per cent) came under observation during the fourth decade

Duration of Symptoms—The average length of time that symptoms had been present before the patient came under observation was 17 3 years, and is longer than that which has been reported previously Riggins (1943) gave an estimated duration of 16 4 years, Clark, Hadley and Chaplin (1894) 11 8 years, Ogilvie (1941) 11 years, and Warner (1935) 10 years The individual duration of symptoms varied from two weeks to 48 years, but in only 17 patients was over 34 years Over this range cases were distributed evenly, and it was the same with all the main ætiological factors except primary tuberculosis in which the interval was only 2 7 years, due to 5 of the 12 cases coming under observation as contacts, and 4 having no symptoms

Presence of Symptoms—It would be of interest to know if bronchiectasis due to various ætiological factors was of more or less severe type For this reason the symptoms commonly found in this disease are tabulated in Table II, and the percentage suffering from individual symptoms and signs related to each ætiological factor The descriptive terms used require clarification Thus by constant cough and sputum it is meant that cough and sputum were present regularly every day Hæmoptysis is self-descriptive, and the term "stained sputum" indicates that small quantities of blood mixed with sputum had been coughed up on one or more occasions but that as much as one teaspoonful of blood had never been reported Patients were described as having constant abnormal physical signs if such were present whenever examination was made Clubbing of the fingers was used to define all degrees of this condition from the earliest stages which have been well described by Branwood (1949) to the most advanced Primary tuberculosis was associated with a smaller incidence of symptoms and abnormal physical signs than any other condition There was little difference between the other antecedent factors, after allowance is made for small numbers

Number and Extent of Lobes Affected—The average number of lobes affected with bronchiectasis was 2 6 throughout the whole series, but when primary tuberculosis was the ætiological factor it was only 1 1 lobes The extent of the disease in a lobe was also much less following this cause In the whole series there were 32 patients in whom the total area affected with bronchiectasis was less than that of the smallest lobe (right middle lobe) Of the 12 post-tuberculous cases 7 (58 3 per cent) were of this type, which will be termed segmental in this paper No other factor was responsible for anything like so high an incidence of segmental bronchiectasis

TABLE II

The Number of Cases of Bronchiectasis due to Various Ætiological Factors together with the Percentages in each Group having Certain Symptoms and Signs

Factor	Total No of Cases	Percentage with Symptoms of					
		Constant Cough	Constant Sputum	Hæmo ptysis (not less than ¼ oz)	Stained Sputum	Constant Abn Phys Signs in Chest	Clubbing of Fingers
Pneumonia	71	84 5	80 2	25 3	23 9	73 2	50 7
Pertussis	20	90 0	70 0	20 0	25 0	75 0	35 0
Influenza	4	100 0	100 0	25 0	25 0	50 0	25 0
Infectious diseases of children	6	100 0	100 0	16 6	33 3	100 0	66 6
Bronchitis	18	66 6	66 6	16 6	27 7	72 1	44 4
Cough since infancy	17	94 1	88 2	23 5	29 4	94 1	52 9
Primary T B	12	41 6	25 0		25 0	25 0	8 3
Mustard gas	8	75 0	75 0	12 5	50 0	100 0	75 0
Post operative chest	4	75 0	75 0	50 0	25 0	100 0	25 0
Various	4	75 0	75 0		50 0	75 0	50 0
Unknown	2	50 0	50 0		50 0	50 0	
All causes	166	80 7	73 4	20 4	27 7	74 1	45 1

Recurrent Pneumonia—A patient has been assessed as suffering from recurrent pneumonia if it occurred in addition to the initial illness Fletcher (1935) found that 28 per cent of his patients had been affected in this way, and Perry and King (1940) reported 24 per cent In this series 40 4 per cent suffered from one or more attacks It was found most likely to arise if the initial ætiological factor was pneumonia Primary tuberculosis, on the other hand, was followed by pneumonia on only one occasion

DISCUSSION

No apology is needed for emphasising the importance of the ætiological factors leading to disease Until they are known prevention, so much to be preferred to the alleviation of symptoms or even cure, is difficult or impossible This survey has shown that patients with bronchiectasis may be divided into two main classes those in whom the origin of their illness is known with reasonable certainty, and those where the cause must be adjudged as doubtful or unknown The first group, whose symptoms follow definite illnesses such as pertussis or primary tuberculosis, can to some extent be avoided by a variety of prophylactic measures When pneumonia is already present the need for energetic treatment is well understood and probably effective in reducing the incidence of bronchiectasis, although it may be that a number of severe cases develop bronchiectasis instead of dying The second group, which has been variously treated as of unknown ætiology or arising from recurrent bronchitis or cough since infancy, thus assumes a particular importance as further progress in prevention must await a surer ætiological background Two alternative theories of causation have been held responsible A considerable body of opinion believes that allergy is the main factor and that satisfactory treatment for this state would reduce the incidence of subsequent bronchiectasis Whether allergy is primarily responsible as was thought by Watson and Kibler (1938) and others, or whether it merely renders a concurrent acute respiratory infection more likely to cause bronchiectasis (Davison, 1944) is not certain However, many have been struck by the large number of chronic asthmatics and bronchitics who do not suffer from bronchial dilatation and question whether it is commoner among them than the remainder of the population Those who do not believe that allergy is important consider that superadded pneumonia is responsible for the onset of bronchiectasis in the large majority They point to the difficulty of diagnosing pneumonia without adequate radiological control, and argue that there may be no severe symptoms even if infected collapse follows No definite conclusion can be reached regarding the ætiology of this group, but radiography, if employed at each exacerbation over long periods, should help to provide an answer

A comparison of the ætiological factors found in the present series with those in others, shows certain differences, most of which are probably explained by variation in the methods of classification and the source of material These reasons can hardly account for the high percentage caused by primary tuberculosis (7 3), and mustard gas (4 9) in a general series of bronchiectatics The former is only mentioned as an ætiological factor by Raia (1938), and only isolated cases due to the latter have been recorded It is difficult to understand why they have received so little attention, particularly primary tuberculosis which, noting its frequency (24 2 per cent) among the children, must be a common cause among the older age groups The explanation that these patients as children are usually segregated among the tuberculous is valid, but does not explain their absence from surveys of adults, unless they have been deliberately excluded without mention or their ætiology has ceased to be obvious In favour of the last solution is the observation drawn from this series—that half the children seen to develop bronchiectasis following primary tuberculosis failed, within a few years, to show specific evidence of their ætiology One case each of bronchiectasis following post-radiation pulmonary disease and pulmonary infiltration with eosinophilia were described Neither cause has figured in previous series of bronchiectatics, although they problably will do so in the future, as neither syndrome is rare On the negative side no case was found to follow tonsillectomy

It has not been possible to find a review relating the extent and symptoms of bronchiectasis to the relevant ætiological factors Any such analysis would only be of significant value if large numbers were collected in order that the rarer causes could be compared with the common ones Impressions, however, can be obtained from relatively small series, and in bronchiectasis such impressions have been responsible for building up the sum of knowledge which we have to-day The relation of ætiological factors to the age of onset of symptoms shows that those with bronchiectasis may be divided into two broad groups the first occurring before the age of 10 in which the majority are due to the infectious diseases of childhood, cough since infancy, and primary tuberculosis , the second arising after the age of 10 which is largely caused by pneumonia, chronic bronchitis and various other conditions, many of which belong to the miscellany of aspiration penumonia The age of coming under observation and the duration of symptoms were much the same whatever the ætiology The actual duration of symptoms (17 3 years) was longer than the average reported This may be accounted for, in part by the fact that the severer examples tend to drift to the large hospitals from which most series have been compiled, and also that a considerable proportion of the cases of bronchiectasis in this area are either small in extent or not suffering from marked symptoms The symptoms found varied little whatever the ætiology except with primary tuberculosis, but following this condition they were less marked in every category chosen Moreover, when the number of lobes affected was compared, it was discovered that far fewer lobes were affected in the cases due to primary tuberculosis, and also that the extent of the damage was much less One of the most troublesome complications of bronchiectasis is recurrent pneumonia and before the advent of chemotherapy and the antibiotics the most frequent cause of death (Perry and King, 1940 , Bradshaw *et al* , 1941) When this was related to the ætiological factors it was found to occur more commonly (63 4 per cent) in those who traced their symptoms to pneumonia than any other condition It is interesting to note that primary tuberculosis was followed by pneumonia in only one patient

From the above findings it might appear that bronchiectasis following primary tuberculosis is more benign than when it follows other diseases, but it must be remembered that this disease is usually responsible for small areas of bronchial dilatation only Moreover, partial stenosis of a bronchus, likely to cause some difficulty in drainage, is common in this type of bronchiectasis and rarely associated with the others under consideration For this reason it might be expected that certain complications would be more probable, and indeed have been described by Brock (1950) I think that its apparent benignity in this series is due to the small areas affected rather than to any other reason Most observers have thought that the symptoms caused and the prognosis of bronchiectasis depended particularly upon its extent, though Raia (1938) pointed out that there is a trend to mildness or severity which becomes apparent early in the course of the disease, an observation that may well depend upon the type of inflammatory reaction between the bronchi This trend appears to be mild after primary tuberculosis

I am deeply indebted to Dr F P Lee Lander without whose encouragement this investigation would never have been started, and to Dr Neville C Oswald for his help in preparing the paper My thanks are due to Mr G Kent Harrison in whose department some of the bronchograms were done, to Dr J H L Easton, Physician to the Bedford General Hospital, and to the many general practitioners of the area for their help in referring patients for investigation I am also indebted to Dr E N Moyes who performed many of the bronchograms, and to Dr W C V Brothwood, County Medical Officer for Bedfordshire for his co operation

SUMMARY

(1) A short historical review of some of the factors concerned in the causation of bronchiectasis has been made

(2) During a period of five years all cases of bronchiectasis ascertainable within an area of nearly 150,000 people have been collected together One hundred and sixty-six (137 adults and 29 children) were confirmed by bronchograms, a further 48 cases were diagnosed but not proved by bronchograms, and therefore not included in the detailed analysis

(3) Bronchiectasis followed pneumonia in 50 4 per cent of the adults and 6 9 per cent of the children In comparison with other series these were respectively the highest and lowest figures found

(5) Chronic respiratory catarrh was the only reported abnormality in the history of 20 9 per cent, it was therefore classed as an ætiological factor The relationship of this group to allergy and pneumonia has been discussed

(6) The percentages due to primary tuberculosis (7 3) and mustard gas (5 9) were higher than those previously reported One case followed post-radiation pulmonary disease and one case was associated with pulmonary infiltrations and eosinophilia

(7) The ætiological factors found were correlated with age of onset, age of coming under observation, duration of symptoms, certain symptoms and signs, number of lobes affected, segmental bronchiectasis, and recurrent pneumonia

(8) Onset in the first decade was associated particularly with the infectious diseases of childhood, primary tuberculosis and cough since infancy, and in the following decades with pneumonia and recurrent bronchitis

(9) Little difference was found in the type of bronchiectasis following the various ætiological factors except for primary tuberculosis, which was followed by fewer symptoms and signs, a smaller number of lobes affected, and a higher percentage of segmental bronchiectasis

(10) Recurrent pneumonia occurred most often when pneumonia was the antecedent factor , it arose once only in bronchiectasis following primary tuberculosis

REFERENCES

ALLISON, P R , GORDON, J , and ZINNEMANN, K (1943), *Journ Path Bact* , 55, 465 BONNAMOUR, S , BADOLLE, and GAILLARD, R (1929), " Le Radio-Diagnostic dans les affections broncho-pulmonaires par le lipiodol," p 53, *L'expansion scientifique française*, Paris BRADSHAW, H H , PUTNEY, F J , and CLERF, L H (1941), *Journ Amer Med Assoc* , 116, 2561 BRANWOOD, A W (1949), *Edin Med Journ* , 56, 105 BROCK, R C , CANN, R J , and DICKINSON, J R (1937), *Guy's Hosp Rep* , 87, 295 BROCK, R C (1950), *Thorax*, 5, 5 CARR, D , DENHAM, W E , and SKINNER, E F (1947), *Dis Chest*, 13, 596 CLARK, Sir A , HADLEY, W J , and CHAPLIN, A (1894), *Fibroid Diseases of the Lung including Fibroid Phthisis*, London, C Griffin & Co DAVISON, F W (1944), *Ann Otol* , etc , St Louis, 53, 849 DIAMOND, S , and VAN LOON, E L (1942), *Journ Amer Med Assoc* , 118, 771 ELLIOTT, T R , and DINGLEY, L A (1914), *Lancet*, 1, 1305 EVANS, W A , and GALINSKY, L J (1944), *Amer Journ Roentgenol* , 51, 537 FARRELL, J T Jr (1936), *Journ Amer Med Assoc* , 106, 92 FLETCHER, E (1935), *Journ thorac Surg* , 4, 460 GAIRDNER, W T (1850), *Mon Journ med Sci* , 11, 122 GEE, S (1877), *St Bart's Hosp Rep* , 13, 63 GRAHAM, S , and HUTCHISON, J H (1947), *Arch Dis Childh* , 22, 162 GREEY, P H (1932), *Journ infect Dis* , 50, 203 HARKAVY, J (1941), *Arch intern Med* , 67, 709 HUGUENIN, R , LEMOINE, J -M , and FAUVET, J (1947), *Bull Soc med Hop Paris*, 63, 146 KAMCHORN, N , and ELLIS, A G (1921), *Amer Journ Med Sci* , 161, 525 KENT, E M (1942), *Amer Rev Tuberc* , 46, 524 KESSEL, L , and HYMAN, H T (1928), *Amer Journ Med Sci* , 175, 511 KOHN, J L , and KOIRANSKY, H (1929), *Amer Journ Dis Child* , 38, 258 LANDER, F P L (1947), Personal Communication LANDER, F P L (1950), *Brit Med Journ* , 2, 1486 LIVINGSTONE, J L (1950), Paper read at the Brompton Chest Hospital, London LOEPER, M (1919), *Progr méd* , Paris, p 89 MILLER, H , PINESS, G , FEINGOLD, B F , and FRIEDMAN, T B (1935), *Journ, Pediat* , 7, 768 NICHOLSON, D P (1949), *Arch Dis Childh* , 24, 29 OGILVIE A G (1941), *Arch intern Med* , 68, 395 PASTEUR, W (1908), *Lancet*, 2, 1351 PERRY, K M A , and KING, D S (1940), *Amer Rev Tuberc* , 41, 531 PESHKIN, M M , and FINEMAN, A H (1931), *Amer Journ Dis Child* , 42, 590 RAIA, A (1938), *Amer Journ Dis Child* , 56, 852 RAMSAY, H , and SCADDING, J G (1939), *Quart Journ Med* , 8, 79 RICHARDS, W F (1944), *Tubercle*, Lond , 25, 60 RIGGINS, H M (1943), *Dis Chest*, 9, 5 ROBERTS, J C , and BLAIR, L G (1950), *Lancet*, 1, 386 SMITH, C E , and RUSK, G Y (1927), *Amer Journ Path* , 3, 225 SMITH, D T (1927), *Amer Rev Tuberc* , 15, 352 SMITH, D T (1930), *Arch Surg* , Chicago, 21, 1173 THOMAS, J W , VAN ORDSTRAND, H S , and TOMLINSON, C (1945), *Ann intern Med* , 23, 405 THOMSON, ST C (1914), *Practitioner*, 92, 745 THORPE, E S (1929), *Amer Journ Med Sci* , 177, 759 TUCKER, G (1931), *Arch Otolaryng* , Chicago, 13, 315 WALDBOTT, G L , KAUFMAN, J M , and MERKLE, K J (1950), *Journ Allergy*, 21, 339 WALSH, T W , and MEYER, O O (1938), *Arch intern Med* , 61, 890 WARNER, W P (1935), *Journ Amer Med Assoc* , 105, 1666 WATSON, S H , and KIBLER, C S (1938), *Journ Amer Med Assoc* , 111, 394 WHITWELL, F (1949), Thesis for M D , Lond

CAROTID SINUS SYNDROME AND CAROTID BODY TUMOUR

By W MICHIE, M B , F R C S (Edin), and R G SIMPSON, M D , M R C P (Lond)

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THE following case is of interest in that it illustrates the characteristic manifestations of the carotid sinus syndrome Unusual features are the co-existence of a carotid body tumour and the prompt and complete relief of all symptoms following surgical removal of the tumour

CASE REPORT

A lady now aged 47 started seven years ago to suffer from transient mental " blackouts," *i e* attacks of clouding of consciousness, during which she felt dizzy and faint The attacks recurred three or four times a month, often around the time of menstruation She was invariably standing or sitting when the attacks occurred, and she observed that they were often precipitated by sudden movements of the head—such as stretching up to a high shelf in her draper's shop During the late summer of 1950 the " blackouts " became progressively more frequent, and, up to the time of her admission to hospital in January 1951, there were numerous episodes daily—often twenty or more, scarcely a day passing without incident Throughout the course of the illness there were a dozen or more occasions when the clouding of the sensorium rapidly gave way to loss of consciousness , she would fall to the ground, usually lying pale and motionless for ½-2 minutes, but in four instances, repetitive clonic movements of arms and legs were noted by witnesses Her general health had always been good, apart from sore throats for many years After an attack of tonsillitis fifteen years ago, she noticed a swelling in the right side of the neck, below the angle of the lower jaw , this had persisted, showing little variation in size, and had never been painful or tender

Family history disclosed no important information

On examination she was found to be a stout cheerful person and a good witness The temperature was 98 6° F , the pulse rate 98 per minute, and the B P 170/90 mm Hg The mouth and throat were healthy A firm, discrete and lobulated mass of walnut size was visible and palpable just below the angle of the mandible on the right side (Fig 1) It was not tender, the overlying skin was normal, and the mass was freely movable only from side to side and not vertically The heart was normal Detailed examination of the nervous system did not disclose any important abnormalities The urine contained neither albumin nor sugar Hb 95 per cent (Haldane) The blood Wassermann reaction was negative Spinal fluid showed normal pressure, cell-count and protein content, and a negative Wassermann reaction A radiogram of the chest and an electrocardiogram were normal

INVESTIGATIONS

The close proximity of the swelling in the neck to the carotid sinus suggested the possibility of the patient's symptoms being those of the carotid sinus syndrome, while the mass itself seemed to display the essential clinical characteristics of a carotid body tumour While the patient was lying in bed, firm pressure with the thumb on the tumour caused a dramatic response there was an almost immediate increase in the rate and depth of the respirations, succeeded in a few seconds by an abrupt and profound fall of the blood pressure and heart rate, followed by a prolonged period of cardiac standstill Unconsciousness supervened seven seconds after the onset of the reaction, and persisted for as long as compression was maintained Release of digital pressure at the end of twenty seconds was followed by a prompt return of consciousness together with a gradual restoration of the heart rate and blood pressure to their former levels Pressure on the left carotid sinus caused only slight and temporary slowing of the heart rate and no impairment of consciousness Adequate digital compression on the right side never failed to reproduce this response, the clinical observations being supplemented by continuous electrocardiographic recordings on a direct-writing machine The findings are briefly presented in Figs 2 and 3 All of the deliberately induced reactions were essentially identical, and the subjective sensations noticed by the patient both before and after the periods of syncope were the same as those which she had experienced with her spontaneous attacks Since the tumour

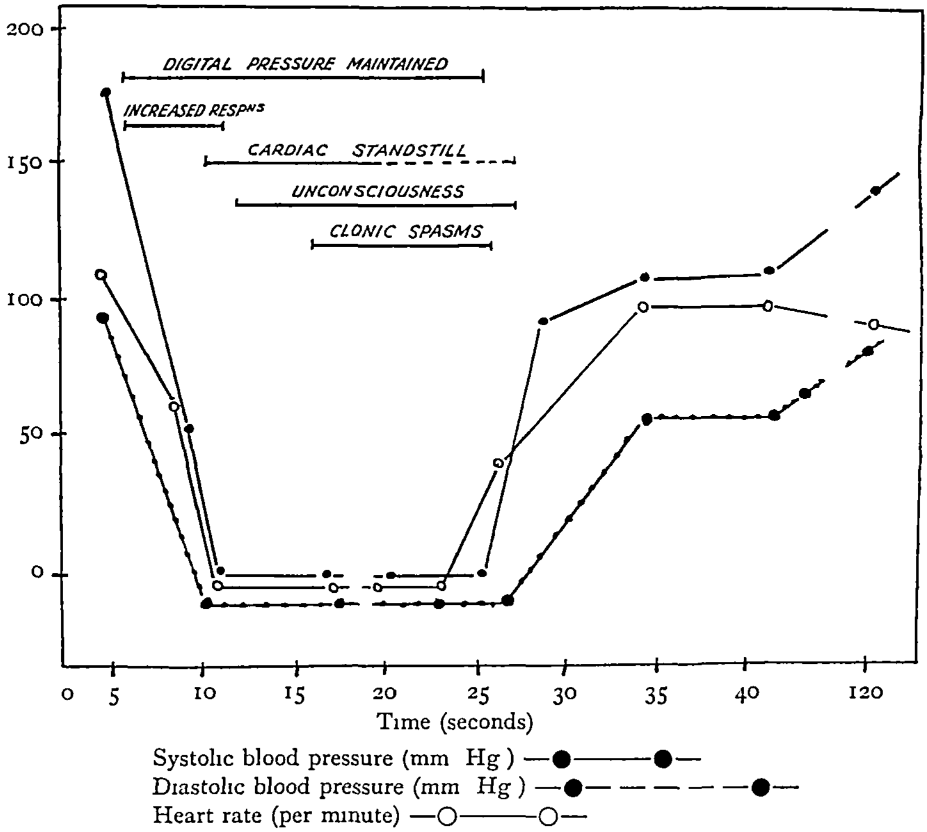

Fig 2 —Diagram showing effects of digital pressure on hypersensitive carotid sinus

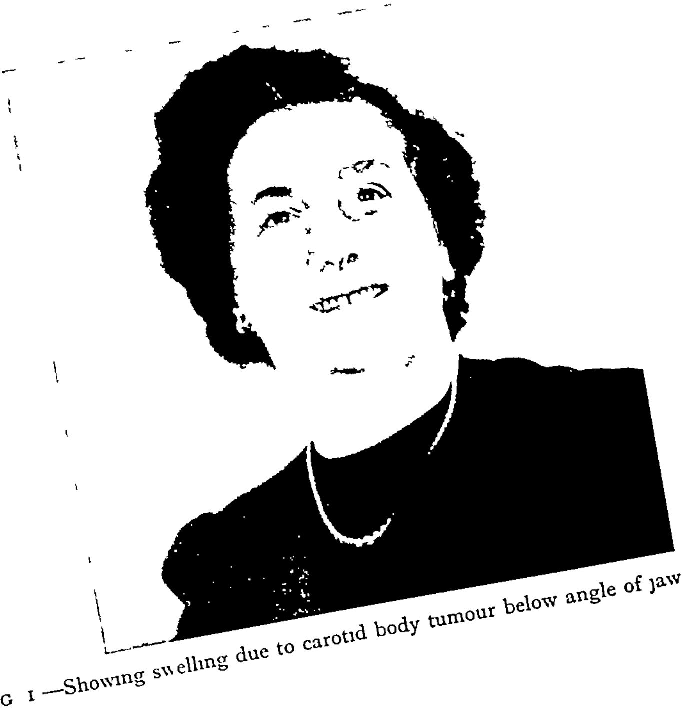

FIG 1 —Showing swelling due to carotid body tumour below angle of jaw on right side

was so situated as to cause pressure on a highly sensitive carotid sinus, it seemed reasonable to expect that surgical removal of the tumour might at least diminish the distressing frequency of the spontaneous attacks In order to explore the possible effects of handling the tumour at operation, digital compression was carried out during a trial period of deep general anæsthesia with thiopentone, nitrous oxide, oxygen and ether A continuous cardiogram showed a slight degree of slowing and irregularity of the heart's action and there was no significant fall in the blood pressure

OPERATION

Deep anæsthesia was induced by the agents previously employed Since the tumour was relatively small and well defined, a generous skin crease incision was used in preference to one along the anterior border of the sternomastoid Following the division of platysma and deep fascia the sternomastoid was retracted backwards and the tumour mass, enveloped by the carotid sheath, was exposed over its entire extent

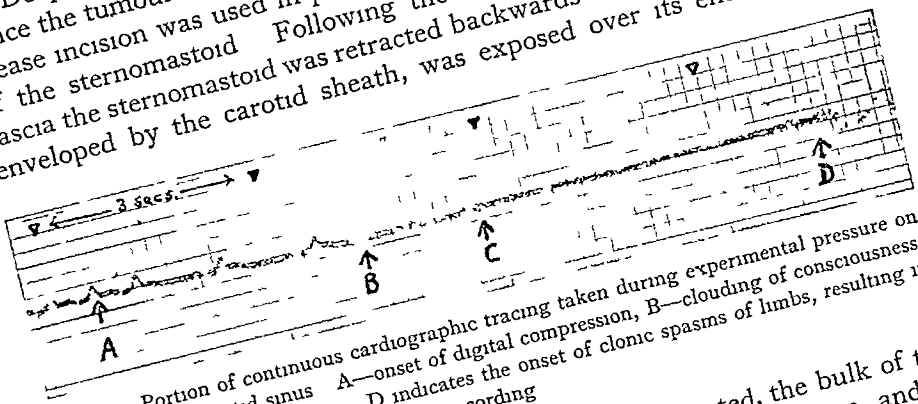

Fig 3—Portion of continuous cardiographic tracing taken during experimental pressure on the right carotid sinus A—onset of digital compression, B—clouding of consciousness, C—loss of consciousness , D indicates the onset of clonic spasms of limbs, resulting in interference with the cardiographic recording

Though the carotid vessels were partially incorporated, the bulk of the tumour lay anteriorly and medially Vascularity was extreme, and as bleeding came mainly from surface oozing, control was limited to swab pressure The main blood-supply derived from the carotid bifurcation and only after the tumour had been dissected free from its attachment to the bifurcation was hæmorrhage completely controlled The internal jugular vein was stretched across the tumour, but was freed by sharp dissection The sympathetic trunk and the vagus and hypoglossal nerves were similarly exposed and preserved

No unusual alterations in respiratory or cardiac function were noted during the operation or in the post-operative period, and subsequent convalescence was uneventful The patient has remained symptom-free since the time of operation On six separate occasions—the most recent being eight months after discharge from hospital—firm pressure on the right and left carotid sinuses separately has failed to produce any significant alterations in respiration, heart rate, blood-pressure, cardiographic record, or the state of consciousness

The Pathological Report on the tumour was as follows —" Macroscopically this specimen appears as a brownish-yellow lobulated and apparently well encapsulated tumour measuring 5 4×3 4×2 cms On one surface the tumour shows a deep Y-shaped groove presumably due to its close relationship to the bifurcation of the common carotid artery The specimen has been bisected and the cut surface is of a fairly uniform greyish-yellow colour intersected by a few irregular greyish coloured, hyaline fibrous bands (Fig 4) Microscopically (Fig 5) the tumour is seen to have a ‘ peritheliomatous ’ pattern—consisting of small clumps of large polyhedral cells, often showing an indistinct outline, with a vacuolated eosinophilic cytoplasm and a large vesicular nucleus usually containing one or more nucleoli and a coarse chromatin network Many of these clumps of cells surround thin-walled vascular sinuses and are themselves separated from each other by compressed vascular spaces lined by endothelial cells There are extensive wide bands of hyaline fibrous tissue and a few focal deposits of hæmosiderin pigment are noted It is considered that this is a carotid body tumour which is histologically benign ”

DISCUSSION

The Carotid Sinus Syndrome—This condition was first fully described as a clinical entity in 1933 by Weiss and Baker, further papers by Weiss and his associates have dealt exhaustively with the clinical aspects of the subject (Ferris *et al* , 1935, and Weiss *et al* , 1936) Since the condition has received comparatively little attention in British literature, it may be useful to give a brief account here of its main features

The essential characteristics of the syndrome are recurring attacks of disordered consciousness almost always associated with transient and profound alterations of the heart rate and blood pressure , the manifestations are those of an exaggerated carotid sinus reflex which is presumed to arise from abnormally sensitive pressure-receptors in the wall of the carotid sinus The present case is a typical example of the remarkably uniform clinical picture seen with this condition It is most common over the age of 45 and tends to affect men more often than women Many of the subjects have signs of arteriosclerosis or hypertension, and the oversensitive sinus can often be palpated because of dilation or local sclerosis, but in a small minority of cases there may be a localised swelling in the neck, most often caused by clinically enlarged lymph nodes, in close relation to the sinus The attacks of impaired consciousness, which usually last for $\frac{1}{2}$-3 minutes, are sometimes initiated by sudden movements of the head or by pressure on the neck, such as may be caused by a tight collar, but frequently such exciting factors are not evident However, digital compression of the oversensitive carotid sinus will almost always confirm the diagnosis by precipitating an attack

Both conservative and surgical methods of treatment are available General measures include the avoidance of sudden head movements

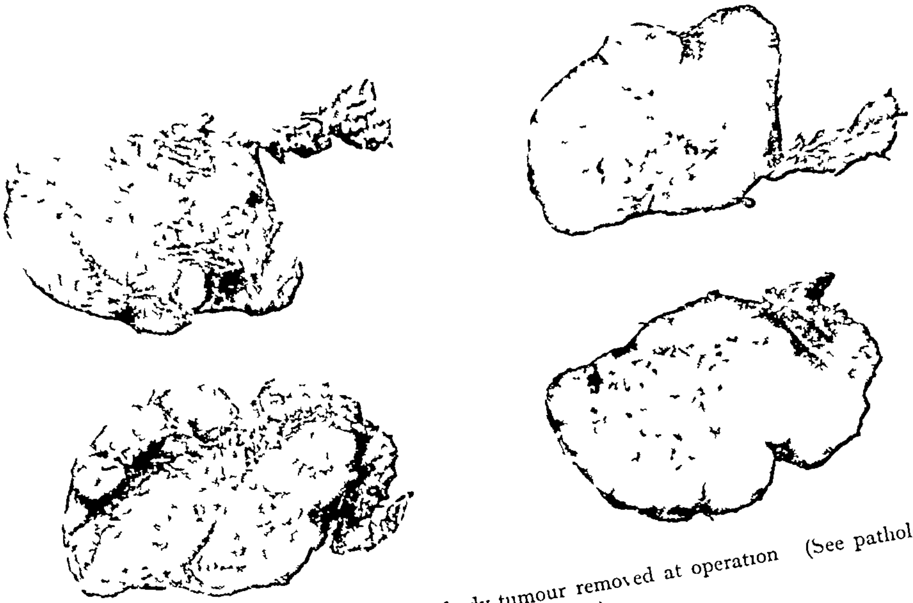

FIG 4—Gross specimen of carotid body tumour removed at operation (See pathological report in text)

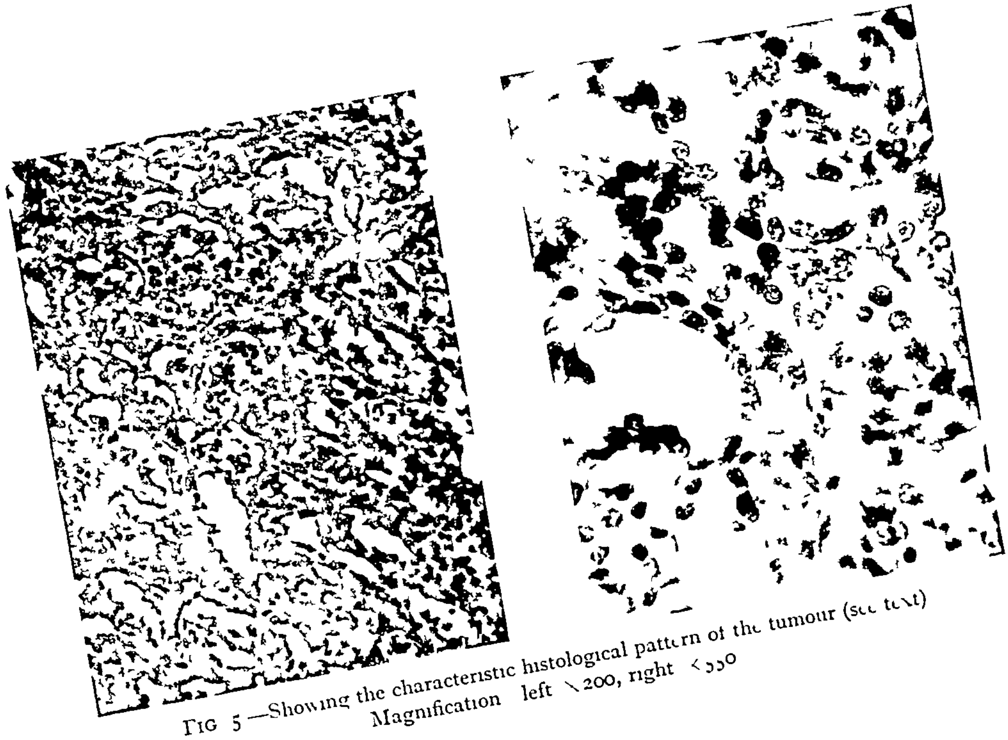

FIG 5—Showing the characteristic histological pattern of the tumour (see text) Magnification left ×200, right ×550

and of tight neckwear In most instances the frequency and severity of the attacks can be diminished or the attacks prevented by the oral use of certain drugs, of which ephedrine hydrochloride ½ grain (0 03 gm) t d s , atropine sulphate 1/120 grain (0 0005 gm) t d s , or tincture of belladonna 15 minims (1 mil) t d s , seem to be the most effective The results of deep X-ray therapy applied to the carotid sinus have not been encouraging Where conservative measures fail to reduce the frequency of attacks, surgical treatment may have to be considered The most effective procedure appears to be surgical denervation of the carotid sinus, which is effected by " stripping " of the sinus and of the common, internal and external carotid arteries for a short distance below and above the sinus , the intercarotid tissue, including the carotid sinus nerve, is also freed and divided

Carotid Body Tumour —There have in all been approximately 300 cases recorded, and the literature has already been adequately reviewed by several authors (Gordon-Taylor, 1940 , Lahey and Warren, 1947, 1951 , Le Compte, 1948 , and Monro, 1950), but the present case is especially worthy of note because the patient suffered from attacks of carotid sinus syncope consequent upon the presence of the tumour This has been reported previously in only three instances, and since the association of syncope with tumour is so uncommon, it would appear that the tumour itself does not play a primary role in the production of syncopal attacks but acts probably by pressing on a hypersensitive carotid sinus The relief of symptoms following removal of the tumour in the present case can probably be attributed mainly to denervation of the sinus caused by stripping of the carotid vessels and of the tissues in the carotid bifurcation during the operation

In conclusion it is suggested that the carotid sinus pressure test may be usefully included in the clinical investigations of those patients who present with a history of recurring mental " blackouts " The test is simple to perform and gives as a rule reliable results, and although it is rarely attended by undesirable effects, caution must be observed with elderly persons in whom unduly prolonged digital pressure should be avoided In these individuals compression should be released promptly on the development of unconsciousness or cardiac standstill, and it is wise to have at hand a syringe containing 8 minims (0 5 mil) liquor adrenaline hydrochloride which may be given subcutaneously should recovery be delayed Adrenaline has been shown by Weiss *et al* (1936) to be capable of aborting most attacks of carotid sinus syncope

SUMMARY

An example of the carotid sinus syndrome in a patient with carotid body tumour is described

Prolonged remission of symptoms has followed surgical removal of the carotid body tumour

The general features of the syndrome are briefly reviewed

The results of various investigations suggest that the symptoms in the present case were caused by pressure of the tumour on an over-sensitive carotid sinus

We wish to thank Dr C D Needham for permission to publish this case and for his helpful criticism For the pathological report and photographs, we are indebted to Dr Douglas Scott of the Department of Pathology, University of Aberdeen

REFERENCES

FERRIS, E B, CAPPS, R B, and WEISS, S (1935), *Medicine*, 14, 377

GORDON-TAYLOR, G (1940), *Brit Journ Surg*, 28, 163

LAHEY, F H, and WARREN, K W (1947), *Surg Gyn Obst*, 85, 281

LAHEY, F H, and WARREN, K W (1951), *Surg Gyn Obst*, 92, 481

LE COMPTE, P M (1948), *Amer Journ Path*, 24, 305

MONRO, R S (1950), *Brit Journ Surg*, 37, 445

WEISS, S, and BAKER, J P (1933), *Medicine*, 12, 297

WEISS, S, CAPPS, R B, FERRIS, E B, and MUNRO, D (1936), *Arch Int Med*, 58, 407

NOTES

Royal College of Physicians of Edinburgh

At the Quarterly Meeting of the College held on Tuesday, 22nd July 1952, the President, Dr W A Alexander, in the Chair, the following were elected Fellows —Daw Yin May, M R C S ENG , L R C P LOND , F R C S E , Maung Shwe Zan, M B EDIN , William John Gibson Barrie, M B E , M D EDIN , James Wright Rae, M B EDIN

The following were elected Members of the College —Anthony Flavien Stanislaus Perera, L M S CEYLON , Mohd Ayub Khan, M B PUNJAB , Walter Sneddon Watson, M D EDIN , William Jonathan Abel, M B EDIN , Nimai Krishna Mitra, M B CALC , Andrew Bogdan, M D LOND , Geoffrey Hugh Templeman, M B E , M D LEEDS , Arthur Jarrett, M B BIRM , Matthew Walter John Boyd, M D BELF , Newton Symonds Chalk, M B QUEENSLAND , Pathiyil Karthiyayani Krishnankutti, M D MADRAS , Sureshwar Prazad Jha, M D PATNA , John Buller Cromie, M D BELF , Henry Gemmell Morgan, M B ST AND , Charles Desmond Ross Pengelly, M B BRISTOL , Harry Altman, M B WITWATERSRAND , Eveline Patricia Forbes, M B CAPE TOWN , Leo Schamroth, M B WITWATERSRAND , Lionel Hugh Mofflin, M B ADELAIDE , Peter George Aungle, M B EDIN , Janet Latta Picken Hunter, M B GLASG

Royal College of Surgeons of Edinburgh

At a meeting of the Royal College of Surgeons of Edinburgh held on 21st July 1952, Professor Walter Mercer, President, in the Chair, the following who passed the requisite examinations were admitted Fellows —Victor Paul Amato, M D UNIV MALTA, 1943 , Manilal Purshottam Amin, M B , B S UNIV BOMB 1945 , Hilla Banaji, M B , B S UNIV BOMB 1945, M D UNIV BOMB 1948 , Amar Chand Bhandhela, M B , B S UNIV PUNJAB, 1944 , Pesi Behramshaw Bharucha, M D UNIV BOMB 1947 , James Alexander Lamb Clark, M B , CH B UNIV EDIN 1941 , Colin James Ross Conacher, M B , B S UNIV SYDNEY, 1944 , Rosemary Helen MacNaughton Davie, M B , CH B UNIV EDIN 1948 , Frederick John Gruar, M B , CH B UNIV NEW ZEAL 1943 , Ahmed Adly Hammouda, M B , CH B UNIV CAIRO, 1942 , Joseph Moise Mayer, M B , CH B UNIV BAGHDAD, 1944, M R C S ENG , L R C P LOND 1950 , Alan Hector Garson Munro, M B , B S UNIV DURHAM, 1935 , Nanalal Ranchhodji Petel, M B , B S UNIV BOMB 1943 , Arthur Douglas Roy, M B , CH B UNIV GLASG 1947 , Max Schaffer, M B , CH B UNIV CAPE TOWN, 1938 , William Seright, M B , CH B UNIV GLASG 1946 , Bertram Leslie Shaff, M B , B CH UNIV WITWATERSRAND, 1946 , Abdel Hamid Shouman, L R C P & S EDIN (TRIPLE) 1942 , Ellis Martin Sparrow, M B , CH B UNIV CAPE TOWN, 1944 , Kenneth Sutherland Stewart, L R C P & S EDIN (TRIPLE) 1944 , John Geoffrey Stonham, M B , B S UNIV MELB 1928, M D MELB 1931 , Willoughby Wilson, M B , B CH QUEEN'S UNIV BELFAST, 1946

Fellows in Dental Surgery

The following candidates having passed the requisite examinations were admitted Fellows in Dental Surgery —David William Dick, L D S , R F P S GLASG 1941, H D D , R F P S GLASG 1950 , John Aird Russell, L D S , R F P S GLASG 1944, H D D , R F P S GLASG 1948

University of Edinburgh

At a Graduation Ceremonial held in the McEwan Hall on Wednesday, 16th July 1952, the following degrees were conferred —

The Degree of Doctor of Medicine—Marion Bowie Bethune, Scotland, M B , CH B (WITH HONS), 1938 (*Highly Commended for Thesis*), John Cecil Cruickshank, Scotland, M B , CH B , 1921 (*Awarded Medal for Thesis*), John Walter Adam Duckworth, England, M B , CH B , 1936 (*Awarded Medal for Thesis*), Robert Alexander Kemp Harper, Scotland, M B , CH B , 1929, Runa Blyth Mackay, Scotland, M B , CH B , 1944, Alan Ramsey Muir, England, M B , CH B (WITH HONS), 1947 (*Highly Commended for Thesis*), Thakur Ram Nath Parhar, India, M B , CH B , 1935, Colin Heriot Macdonald Walker, Scotland, M B , CH B , 1946

The Degree of Doctor of Philosophy—In the Faculty of Medicine—Bruce Cruickshank, M B , CH B , Zbigniew Godlowski, M D (CRACOW), M R C P (ED), Ronald Haxton Girdwood, M B , CH B (WITH HONS), F R C P (ED), M R C P (LOND), Autar Singh Paintal, M B , B S , M D (LUCKNOW), Lilli Stein, M A (CANTAB)

The Degrees of Bachelor of Medicine and Bachelor of Surgery—David Hume Adamson, Scotland, James Charles Aickin, New Zealand, John Alexander Aitken, Scotland, Norman Colvin Allan, Scotland, Harry Cochrane Allen, England, Anne Johnston Anderson, Scotland, Andrew Armstrong, Scotland, Evan Francis Auden, Jamaica, Timothy Awuku-Asabre, Gold Coast, Wiliam McAlpine Ayles, Scotland, John Alexander MacDonald Bain, Scotland, Arthur Banks, England, Frank Macrae Begg, Scotland, William Duncan Bennett, Scotland, Alastair James Berry, Scotland, Hugh Sharp Polson Binnie, Scotland, Sheila Hamilton Birse, Scotland, Gerald Claverton Biss, England, Alexander Bisset, Scotland, Allan Black, Scotland, James George Blyth, Scotland, Heather Bremner, Scotland, Alison Grace Hilda Brown, Scotland, Jean Forbes Brown, Scotland, Donald Budge, Scotland, Douglas Cadger, Scotland, Helen Maclean Caldwell, Scotland, Hamish Argyll Campbell, South Africa, David Ian Bell Carrie, Scotland, Thomas Meredith Chalmers, Scotland, Dennis Gerard Chambers, England, Agnes Clark, Scotland, Henry Grosvenor Clarke, B SC (LOND), England, Allan Craig, Scotland, Margaret Cramb, Scotland, Findlay McDonald Robertson Cranston, Scotland, George Alexander Graham Crease, Scotland, Samuel Howard Davies, England, Kenneth John Dennis, Scotland, Margaret McCombie Dewar, Scotland, Agnes Main Dickson, Scotland, Andrew Doig, Scotland, Peter Holt Dootson, England, Betty Duncan, Scotland, James Kelman Edwards, Scotland, William Alexander Elliott, Scotland, Edward Thomas Faunch, England, William Ferguson, Scotland, John Alistair Duncan Gillies, Scotland, Joyce Yvonne Graham, Scotland, Robert William Graham, Scotland, Michael John Grayson, England, William Moncrieff Haining, Scotland, Daphne Veronica Marjorie Halliday, Scotland, William Harrison, Scotland, Pamela Percival Hartley, England, George Izatt Hendry, Scotland, Rena Elizabeth Hogg, Scotland, James Hood, Scotland, Margaret Hope, Scotland, Agnes Campbell Howie, Scotland, Constance Catherine Mary Howie, Scotland, George Anthony Ives, England, Thomas Peter Carlton Jameson, England, Victor Walker Johnston, England, Septimus Matthys Joubert, M SC (STELLENBOSCH), South Africa, Lilias Kilpatrick, Scotland, Christine Catherine Graham Krause, Scotland, Mairi Hodgkinson Lack, Scotland, John Patrick Laidlaw, Scotland, Richard Baillie Laidlaw, Scotland, Ann Leslie Langley, England, Adam William Blyth Lawson, Scotland, William Joseph Hannay Leckie, Scotland, Peter Brotherston Lesslie, Scotland, Charles Donald Livingstone, Scotland, Margaret Allison Loraine, B SC, Scotland, Ian Alexander Lowe, Scotland, George Ballantyne McAulay, Scotland, Hugh Fraser MacConnachie, Scotland, Alexander McDonald, Scotland, Hamish John McDonald, Scotland, Hugh Macdonald, Scotland, Isobel Macdonald, Scotland, Jean Murray Macdonald, Scotland, Robert Macdonald, Scotland, Gerald Patrick McGovern, Scotland, David Paterson McGowran, Scotland, Duncan MacGregor, Scotland, Kathleen Leslie MacGregor, Scotland, George Meiklejohn McLaren, Scotland, John Macleod, Scotland, Murdo Macleod, Scotland, Inez Melrose McMurray, Scotland, John McNae, Scotland, Ian Simpson McRobbie, Scotland, Ronald Gibson Mahaffy, Scotland, John Mein Main, Scotland, John Edward Malcolm, Scotland, Charles Matheson Manson, Scotland, Thomas Williamson Manson, Scotland, Frederick Peter Sefton Marriott, England, John Archibald King Meikle, Scotland, Keith Thomas Wyndham Miller, B SC, Scotland, William Howell Morgan, Wales, James Kinnear Morrison, B SC, Scotland, Norman McQueen Munnoch, Scotland, Dorothy Murphy, Scotland, Peter James Brodie Murray, Scotland, Gerald John Matthewson Nairn, New Zealand, William Jeffrey Newlands, Scotland, Paulette O'Dowda, England, James Noel Park, M A, Scotland, Morag (*nee* MacQuarrie) Parnell, Scotland, Richard Albert Parry, England, Alan Bernard Partridge, M A (CANTAB), England, Margaret Dewar Paton, Scotland, Ronald William Fordyce Paul, Scotland, William Frederick Paveley, England, William Peter, Scotland, Renos Charalambous Phellas, Cyprus, David Edward Baden Powell, Wales, Harry William Singer Rankin, Scotland, Jean McKay Reid, Scotland, Kathleen Mary Robb, Scotland, Michael Kefford Robinson, England, Andrew Isdale Ross, Scotland, Ian Alexander Bruce Mackenzie Ross, B A (CANTAB), Scotland, Thomas Allan Sanderson, Scotland, Peter Dodge Sears, England, Marjorie Elizabeth Joan Shafto, Scotland, Doreen Walker Shennan, Scotland, John Patrickson Shutt, England, Basil Crandles Smith Slater, Scotland, William Denney Smith, Scotland, Alastair Kenneth Morrison Stewart, Scotland, Frederick Lindsay Sturrock, Scotland, James Herkes Tait, Scotland, David Ernest Meguyer Taylor, England, Joseph Arthur Taylor, England, Ian Moyes Thom, Scotland, Colin Hugh Thomson, Scotland, Edward David Macrae Tod, England, Ian Carnochan Kerr Tough, B SC, Scotland, George Henry Wallace, Scotland, George Scott Wallace, Scotland, Alexander Watt, Scotland, Gilbert Owen Way, England, David Bamford Williamson, England, John Boyd Willliamson, D S C, Scotland, Alan Oliver Arneil Wilson, Scotland, James Wilson, Scotland, Henry William Wright, Scotland

Diploma in Public Health—Edwin Crighton Byrom Bramwell, M B, CH B, Isobel Beatrice Craighead, M B, CH B, James Drummond, M B, CH B, Robert Reid Gillies, M B, CH B, Robert Stevenson Hardie, M B, CH B, Margaret Graham Martin, M B, CH B, Elizabeth Christina Nelson, M B, CH B, John Hunter Nicolson, M B, CH B, Robert Park, M R C S (ENG), L R C P (LOND), Dattatraya Krishava Ramadwar, M B, B S (CALCUTTA), Shafiqur Rehman, M B, B S (PUNJAB), William Serle, M B, CH B, Charles William Shearer, M B, CH B, Claud Edmund George Wickhan, M B, B S (LOND), Ian Macaulay Wood, M B, CH B, Harold William Woolner, L R C P (ED), L R C S (ED), L R F P AND S (GLASG), Eric Walter Wright, M B, CH B

Diploma in Tropical Medicine and Hygiene—Ahmad Mohamed Ishak El Haddad, M B, CH B (CAIRO), Duncan Murray Cameron, M B, CH B, Duncan Gordon Conacher, M B, CH B, Aisha Zaki Shafei Hanno, M B, CH B (ALEXANDRIA), William Kofie Lutterodt, M B, CH B, Yahia Marzouk, L R C P (ED), L R C S (ED), L R F P AND S (GLASG), Hareebrun Bunsee Singh, L R C P (ED), L R C S (ED), L R F P AND S (GLASG), Chengleput Harikrishnan Sivaraman, M B, B S (MADRAS)

Diploma in Psychiatry—Beatrice Margaret Allen, M B, CH B, David Satya Nand, M B, B S (LAHORE)

Sister-Tutor Certificate—Rosanna Cunningham, Dora Helen Marguerite Bailey, Hilda Baker, Jean Mima Barr, Agnes Walker Macdonald Boag, Kathleen Brennan, Olga Helen Brunton, Catherine Nicoll Dallas, Mary Josephine Doherty, Erica Dorothy Garner, Joseph Green, William Arthur James, Douglas McArdle, Frank Finlay Maconaghie, William McGrath, Mary Maciver, Dorothy Marsden, Nora Marsh, Jessie Monteath, Margaret Barr Muir, Nora Pillion, Agnes Vallance Rae, Mary Rankin, Hilda May Saunders, Martha Granger Shout, Kathleen Jean Wallace Wilson

Certificate in Medical Illustration—Sheila Yzetta Calvert Mackie

Awards of Scholarships, Bursaries, Prizes, etc—*The Cameron Prize in Practical Therapeutics*—Karl Paul Link, PH D, Professor of Biochemistry in the University of Wisconsin, in recognition of his work on anti-coagulant therapy *The Ettles Scholarship and Leslie Medal*—Samuel Howard Davies, M B, CH B *The Scottish Association for Medical Education of Women Prize*—Alison Grace Hilda Brown, M B, CH B *The Dorothy Gilfillan Memorial Prize*—Alison Grace Hilda Brown, M B, CH B *The Stark Scholarship in Clinical Medicine*—John Patrick Laidlaw, M B, CH B *The James Scott Scholarship in Obstetrics and Gynæcology*—James Kinnear Morrison, B SC, M B, CH B *The Buchanan Scholarship in Obstetrics and Gynæcology*—Samuel Howard Davies, M B, CH B *The Mouat Scholarship in the Practice of Physic*—Samuel Howard Davies, M B, CH B *The Beaney Prize in Anatomy and Surgery*—Samuel Howard Davies, M B, CH B *The Gunning Victoria Jubilee Prize in Anatomy*—Alan Ramsay Muir, M D *The Lawson Gifford Prize in Obstetrics and Gynæcology*—David Ernest Meguyer Taylor, M B, CH B *The Keith Memorial Prize in Systematic Surgery*—David Ernest Meguyer Taylor, M B, CH B *The Conan Doyle Prize*—Septimus Matthys Joubert, M SC (STELLENBOSCH), M B, CH B *The Wightman Prize in Clinical Medicine*—Marjorie Elizabeth Joan Shafto, M B, CH B *The Annandale Medal in Clinical Surgery*—Pamela Percival Hartley, M B, CH B *The Royal Victoria Hospital Tuberculosis Trust Medal*—Samuel Howard Davies, M B, CH B *The Murdoch Brown Medal in Clinical Medicine*—John Patrick Laidlaw, M B, CH B *The Colonel Thomas Biggam Memorial Medal and Prize in Pathology*—James Syme *The George Guthrie Research Fellowship in Child Health*—Thomas Theodore Scott Ingram, M B, CH B *The Freeland Barbour Fellowship*—Rachel Brodie Mackay, M B, CH B *The Ethicon Research Fellowship*—Sarashi Ranjan Mukherjee, M B, B S (CALCUTTA) *The Whaitt Research Scholarship*—Henry Bruce Torrance, M B, CHB *The Paterson Travelling Scholarship in Surgery*—Hugh Arnold Freeman Dudley, M B, CH B *The Wilkie Surgical Research Scholarship*—Edmund Joseph Delorme, M D (TORONTO) *The Crichton Research Scholarship*—Rachel Brodie Mackay, M B , CH B *The Wellcome Medal and Prize in the History of Medicine*—George Dick Forwell, M B , CH B *The Ellis Prize in Physiology*—Krechimir Krnjevitch, M B , CH B , B SC

An Address to the new Graduates was delivered by the Promoter, Professor George Hector Percival, M D , PH D , F R C P (ED)

Triple Qualification Board

THE examinations of the Board of the Royal College of Physicians of Edinburgh, the Royal College of Surgeons of Edinburgh, and the Royal Faculty of Physicians and Surgeons of Glasgow have just concluded at Edinburgh The following passed the Final Examinations, and were granted the diploma of L R C P EDIN , L R C S EDIN , L R F P AND S GLASG —Ranjit Singh Ahluwalia Mavis Fay Anderson, Frederick Jacobus Badenhorst, James Brown Barnett Baird, Carl Edgar Barth, George Alan Christie Binnie, Edwin Henry Brown, Dennis Gerard Chambers, Brian Cornes, William Armstrong Dalgleish, Eric Albert Ehlinger, Sydney Fogel, Brenda Gale, Colina Graham, Ruth Esther Graham-Yooll, Jean Marie Henri Roland Hardy, Arthur Rowland Isaac, Amirali Husein Kassam, Viljoen Kritzinger, Claude Hamilton Lalgee, Pamela May Lambden, Peter Angus Lowe, William Allan Mahon, Pearl Kallman Malasky, Christine Wallace Mann, Robert William Stuart Miller, Eric Campbell Moffat, James Ian Morrison, John Aikman McIlvride, Agnes Forrest Mackay, Arbold Orwin, Joyce Elizabeth Anne Ovens, Hedwig Marianne Martha Papigay, Audrey Pilbeam, Jean Margaret Price, Raymond Alfred William Ratcliff, Margaret Helen Rodger, Enid Sagar, Ralph Shabetai, Thelma Dorothy Standing, Robert Steele, Alexander Stevenson, Cyril Ward, Martin Herbert Weinberg, Milton Meyer Weiner

NEW BOOKS

Diseases in Old Age—A Clinical and Pathological Study of 7941 *Individuals Over* 61 *Years of Age* By ROBERT T MONROE, M D Pp xi+407 London Geoffrey Cumberlege 1952 Price 32s 6d net

The increasing proportion of old people in the population has opened up a whole new field both in medicine and social medicine In this book the author has surveyed the clinical, pathological and therapeutic material from 7941 elderly persons admitted to the Peter Brent Brigham Hospital The diseases of each system are analysed completely and are summarised at the end of each chapter This work is a very good attempt to establish a basis for geriatrics as a definite and separate branch of medicine The book should be read by all those interested in this subject

The Management of Bronchial Asthma By HERBERT G J HERXHEIMER, M D Pp viii+107, with 16 illustrations London Butterworth 1952 Price 22s 6d net

Dr Herxheimer has written an individualistic and up-to date review of a subject on which he is an acknowledged authority On drug treatment he presents new ideas which, although they may not receive universal approval, merit further investigation and clinical trial He believes that the anti-histamine drugs, in selected cases, are more useful than is generally recognised Acquired tolerance to adrenaline, ephedrine and similar drugs, and methods of dosage designed to avoid it, are discussed in detail This review, unlike most on the same subject, strikes a note of therapeutic optimism which should prove refreshing to consultant and general practitioner alike

Modern Practice in Tuberculosis Edited by T HOLMES SELLORS, M A, D M, M CH, F R C S, and J L LIVINGSTONE, M D, F R C P Volume I, pp xxviii+355, with 105 illustrations Volume II, pp vii+441, with 161 illustrations London Butterworth 1952 Price £7, 7s

In 29 chapters, written by 39 experts, these volumes cover the morbidity and mortality statistics of tuberculosis, pathogenesis, morbid anatomy, practical bacteriology, B C G, social problems, the psychology of the tuberculous, and clinical and therapeutic aspects of pulmonary tuberculosis There are also chapters on tuberculosis of the lymph glands, abdominal organs, bones and joints, central nervous system, pericardium, skin, eye, and genito urinary system, besides an article on sarcoidosis Most of the contributors come from the United Kingdom and on the whole the book reflects current British thought Anyone interested in tuberculosis will read the book with pleasure and there will be few who do not learn a great deal from it The standard of production is high, the illustrations are clear and, considering the number of authors, it is remarkable how consistently readable are their contributions

The different contributors have attacked their tasks in varying manners Many have done original work in the particular subject they write about and some of these give undue weight to their own views to the exclusion of opposing argument But their views are always worth close attention and on the whole there is far more fact and far less vague opinion in these volumes than in many similar works Among a number of outstanding contributions, Dr Cruickshank's chapter on the quantitative bacteriology of sputum conversion, Dr Clegg's on morbid anatomy, Dr Tattersall's on chest clinics, Dr Richards' on tracheo-bronchial tuberculosis and Sir Hugh Cairns and Dr Honor Smith's on tuberculous meningitis are particularly noteworthy It is perhaps a pity that there is no chapter on methods of research in tuberculosis, a subject to which the British school has made notable contributions, but in general it is difficult to quarrel with this outstanding book

The Life and Work of Astley Cooper By R C BROCK Pp 176, with 14 illustrations Edinburgh E & S Livingstone 1952 Price 20s

Every reader of this excellent biography will agree that the time had come for a reassessment of Astley Cooper's achievement in the world of surgery Since Bransby Cooper published the two-volume life of his uncle, in 1843, little has been done to honour the memory of the great surgeon who was so worthy a successor to John Hunter The son of a clergyman of Norfolk, Astley Cooper became a student at Guy's and St Thomas's Hospitals, then closely linked, and he lived in the house of Mr Henry Cline, whose surgical teaching was an important influence in his life Another influential teacher was Alexander Monro (secundus), under whom Cooper studied during seven months' residence at Edinburgh, and to whom he later dedicated his treatise on Hernia, in 1807 Astley Cooper was already well known as anatomist and surgeon when he was appointed Surgeon to Guy's Hospital in 1800 His skill as an operator, combined with his immense energy and industry, soon carried him to the peak of success as the leading surgeon of his day As might be expected, some of the stories which lend such colour to the previous biography are repeated in this smaller book episodes of the faithful though mercenary butler " Charles," of the dissection of an elephant in the courtyard of Cooper's house, of the removal of a sebaceous cyst from the head of George IV—a risky proceeding in the pre-antiseptic days A full account is given of Astley Cooper's pioneer work in arterial surgery, including his ligature of the aorta It is interesting to note that in 1817 he tied the femoral artery, using a catgut ligature, cutting the ends short, and closing the wound, which healed by first intention This was fifty years before the time of Lister, who is usually regarded as the first to use catgut as a ligature Lister made its use safe, but Astley Cooper was first to use it The writer has done well to recall the work of one who did much to advance the science of surgery and to carry on the Hunterian tradition It is a book which every medical man should read

Fœtal and Neonatal Pathology By J EDGAR MORISON 1952 Pp xi+366, with 59 illustrations London Butterworth Price 50s

This is an important contribution to a subject on which there has been for long need of a modern book The emphasis is on those factors that may affect the developing fœtus and the ability of the newborn infant to adapt itself to postnatal life The author believes that advance in knowledge must be made by research in these fundamental aspects of fœtal pathology, rather than by studies based on routine autopsies, and the discussion of the present state of knowledge in this respect is illuminating and excellently done He has rendered a useful service in his lucid and readable review of many confused and controversial aspects of fœtal and neonatal physiology, in their bearing upon the development of pathological states The section on infection is also useful and informative The least satisfactory feature is the actual description of pathological processes These are often sketchy, and not adequately illustrated This decreases the value of the book as a work of reference for the use of a pathologist finding his way in this, to many, unfamiliar field of pathology, and seeking guidance in the carrying out of his routine autopsies The bibliography is large and well chosen

A New Outlook on Mental Diseases By F A PICKWORTH, M B, B S, M R C S, L R C P Pp 304, with 24 plates, 4 illustrations Bristol John Wright Price 60s net

The book, written by a pathologist, is a tribute to the work and enthusiasm of Dr T C Graves, Birmingham, who concerned himself so greatly with the investigation and treatment of chronic sepsis in all types of mental disorder

Dr Pickworth has formulated his own views on the basis of his pathological work and has suggested that a proper understanding of the mind and its disorders can only be determined by a disturbance of the vascular system due to chronic toxic infective conditions He attempts to defend and substantiate this position by his own work and by numerous uncritical quotations from the work of others Dr Pickworth brushes aside the possibility of any other approach to the understanding of these most complex disturbances His book, therefore, is an example of biassed pleading and dogmatic assertion to a degree that is almost embarrassing He so simplifies the issues as to make his position untenable

Under these circumstances it is impossible to recommend this book as a guide or stimulus either to medical students or to the trained psychiatrist

The Apologie and Treatise of Ambroise Pare, containing the Voyage made into Divers Places, with many of his Works upon Surgery Edited by GEOFFREY KEYNES Pp 227, with four full-page illustrations and a number of woodcuts London Falcon Educational Books Price 15s

Among the medical classics of early times which may still be read with pleasure and profit none ranks higher than the *Works of Ambroise Pare* What Vesalius accomplished for anatomy, what Harvey did for physiology, Pare set forth in the field of surgery, and became one of the greatest surgeons of all time His graphic account of his campaigning days is a joy to read, so full is it of action, adventure and humour To have it now presented in so handy, clear and inexpensive a form is a great advantage, and the sponsorship of so eminent a bibliographer as Mr Geoffrey Keynes is in itself a guarantee of excellence The second half of the book is devoted to selections from the surgical writings of the master, dealing with hernia, with "wounds made by gunshot, other fierie engines, and all sorts of weapons," with mummie as a remedy, with amputations and fractures and cataract, with cutting for the stone, and the use of bezoar, and finally to end the fine collection, an essay on "How to make reports," from which even the modern recorder may glean some helpful advice The volume is illustrated by four full page portraits of Pare, and by a selection of the original woodcuts This well timed reproduction of a classic may be cordially recommended, not only to the surgeon and medical student, but also to the general reader who will find in it a vivid picture of a stirring time

NEW EDITION

The Rhesus Factor By G FULTON ROBERTS, M A , M D Third Edition Pp vii+90
London William Heinemann 1952 Price 5s net

First appearing in 1947 this little book is now in its seventh printing—evidence of its popularity and usefulness This new edition, still intended as a brief and elementary survey, has been increased by the addition of two new chapters and by short notes on other blood groups It has been thoroughly brought up to date and should be of the greatest assistance to the clinician in dealing with hæmolytic disease

BOOKS RECEIVED

BAILEY, HAMILTON, F R C S (ENG), F A C S , F I C S , F R S E , and LOVE, R J MCNEILL, M S (LOND), F R C S (ENG), F A C S , F I C S A Short Practice of Surgery Ninth Edition (*H K Lewis & Co Ltd , London*)	55s net
BROTHERSTON, J H F , M A , M D , D P H Observations on the Early Public Health Movement in Scotland (*H K Lewis & Co Ltd , London*)	21s net
CLAYTON, E B , M B , B CH (CANTAB) Electrotherapy and Actinotherapy Second Edition (*Baillière, Tindall & Cox, London*)	16s net
COLLINS, VINCENT J , M D Principles and Practice of Anesthesiology (*Henry Kimpton, London*)	75 net
DECKER, ALBERT, M D , D O G , F A C S Culdoscopy (*W B Saunders Company Ltd , London*)	17s 6d
GARDNER, ERNEST, M D Fundamentals of Neurology Second Edition (*W B Saunders Company Ltd , London*)	24s
Edited by HEWITT, RICHARD M Collected Papers of the Mayo Clinic and the Mayo Foundation Volume XLIII (*W B Saunders Company Ltd , London*)	60s net
JOHNSON, JULIAN, M D , D SC (MED), and KIRBY, CHARLES K , M D A Handbook of Operative Surgery of the Chest (*The Year Book Publishers Inc , Chicago*)	68s
KEMP, TAGE, M D Genetics and Disease (*Oliver & Boyd Ltd , Edinburgh*)	60s net
LAKE, NORMAN C , M D , M S , D SC (LOND), F R C S (ENG) The Foot Fourth Edition (*Baillière, Tindall & Cox, London*)	25s net
Edited by LANSING, ALBERT I , PH D Cowdry's Problems of Ageing Third Edition (*Baillière, Tindall & Cox, London*)	114s net
LEOPOLD, SIMON S , M D The Principles and Methods of Physical Diagnosis (*W B Saunders Company Ltd , London*)	37s 6d
MONCRIEFF, ALAN, M D , F R C P , and THOMSON, WILLIAM A R , M D Child Health Second Edition (*Eyre & Spottiswoode, London*)	21s net
MUNRO, DONALD, M D , F A C S Injuries to the Nervous System (*W B Saunders Company Ltd , London*)	37s 6d
PUNT, NORMAN A The Singer's and Actor's Throat (*William Heinemann, London*)	10s net
RITVO, MAX, M D , and SHAUFFER, I A , M D Gastrointestinal X Ray Diagnosis (*Henry Kimpton, London*)	£7, 10s net
SHAFFER, CARL F , M D , F A C P , and DON, W CHAPMAN Correlative Cardiology (*W B Saunders Company Ltd , London*)	47s 6d net
Edited by WOLSTENHOLME, G E W , O B E , M A , M B , B CH Ciba Foundation Colloquia on Endocrinology Volume II (*J & A Churchill Ltd , London*)	35s net
WRIGHT, SAMSON, M D , F R C P Applied Physiology Ninth Edition (*Oxford University Press, London*)	50s net
Advances in Medicine and Surgery from the Graduate School of Medicine of the University of Pennsylvania (*W B Saunders Ltd , London*)	40s net

Edinburgh Medical Journal

October 1952

THE RETICULOSES AND LYMPHORETICULAR SARCOMAS FROM THE RADIOTHERAPIST'S POINT OF VIEW

By MARGARET C TOD

WHEN I took the reticuloses as my subject I found that if I were to make the best use of the material provided by the case records of the Christie Hospital it would be necessary to include a large group of anaplastic radiosensitive tumours which are not true reticuloses but sarcomas or even, possibly, carcinomas I also decided that it would be most useful if I gave most of my time to the commoner conditions and refrained from descriptions of single cases however rare and unusual It was tempting to study the strange forms taken by some of these hyperplasias of lymphoreticular tissues, their spectacular complications such as skin lesions, their rapid progress and even, occasionally, their unexpected cure, but each case is almost unique and experience with one gives little help for the next I am a radiotherapist with treatment my main concern, and the results of treatment can only be assessed if numbers are available which allow statistical evaluation For this, wide grouping is needed, and that which I shall suggest is used to try to find out how present methods of treatment can most usefully be applied

Reticulosis is a name applied to certain forms of neoplasia which appear to be multifocal in origin and have characteristic symptoms of systemic disturbance When the true sarcomas of lymphoid tissue are included, whether they be differentiated or anaplastic, the term lymphoreticular neoplasia is more accurate For purposes of this discussion I have regarded the following pathological reports as indicating the presence of a reticulosis or lymphoreticular neoplasm , Hodgkin's disease or lymphadenoma, Brill-Symmer's disease or lymphoid follicular reticulosis, leukæmia, lymphosarcoma, reticulum cell sarcoma, anaplastic sarcoma, and cases with such doubtful reports as " anaplastic tumour, may be either sarcoma or carcinoma " This list is incomplete but it follows my declared intention to deal only with common conditions

PATHOLOGY

There is no group of diseases about which more uncertainty exists Their ætiology, their nature and their manifestations are all subjects of dispute, and the difficulty of making a definite diagnosis from histological material obtained by biopsy is well known During the last 30 years there have been a series of phases which might be described as changes of fashion in nomenclature At one time the theory that all the conditions here described as reticulosis were infective granulomas held the field, and the word sarcoma was seldom used Next the pendulum swung back to the idea of neoplasia and many cases of Hodgkin's disease which had become malignant were called polymorphic or reticulum cell sarcoma Then came the classification by Robb Smith, excellent in that it drew attention to how the cells grow in the affected nodes, but too elaborate for every day use and now seldom seen in the reports we receive Finally, during the last few years there has been a return to the use of names, and we have Hodgkin's disease, Brill-Symmer's disease, Schuller-Christian disease and the Letterer Siwe syndrome Often the report on the named disease is qualified by saying that it is atypical or by phrases implying uncertainty or offering a choice of diagnosis A new difficulty has also arisen regarding the true nature of some anaplastic tumours, and cases with multiple enlarged lymph nodes, showing all the clinical signs we associate with reticulosis, may be reported as anaplastic or even as transitional cell carcinoma secondary to an unknown primary

My own belief, and that on which we base our concept of these diseases, is that they form one continuous spectrum of neoplasia on which stand out peaks consisting of tumours of distinct recognisable character The theory that all these tumours form one spectrum is related to their common origin in the primitive mesenchyme, the provider of the stem cells for all differentiated lymphoreticular tissue This follows the teaching of Dawson, Innes and Harvey[1] of the Edinburgh school, who speak of " The stem cell of lymphoid tissue having *in situ* the productive potentialities of endothelioblast, fibroblast and lymphoblast " Clearly such a cell could give rise to tumours differing greatly in appearance but of similar basic character Willis[2] also accepts this theory of origin and writes of " The chaos of names which has developed in the attempt to identify and separate the neoplasms of lymphoid tissue when all are only variants with many transition forms and capable of being changed from one to another " He allows that certain types, Hodgkin's disease, reticulum cell sarcoma or Brill-Symmer's disease are sufficiently differentiated to show definite character He stresses, however, the importance of the completely undifferentiated tumour and says, " A completely anaplastic sarcoma is indistinguishable by microscopic study alone from any other completely anaplastic growth "

Here is a border line where confusion between sarcoma and carcinoma certainly occurs This adds to the difficulty of some radiotherapists who have come to attach great importance to the differing sensitivity of mesodermal and epidermal tumours and expect the pathologist to distinguish between them On this point Willis says, " I repeat my conviction that excluding tumours sufficiently differentiated for positive histological identification there is no type of structure alleged to be characteristic of any form of sarcoma or endothelioma which may not be perfectly imitated by areas of atypical carcinoma " Writing of this lack of distinction in their discussion of lymphœpithelioma Harvey, Dawson and Innes,[3] after mentioning the points by which carcinoma might be separated from sarcoma say, " Neither architecture nor cytology is sufficiently distinctive " and conclude that many so-called lympho-epitheliomas are actually reticulum cell sarcomas If this is true, it must be a waste of time to try to separate the anaplastic tumours, but positive identification, when possible, remains of great importance, and the presence of this intermediate zone of indeterminate tumours does not excuse lack of knowledge of the changes which follow differentiation either towards true connective tissue sarcoma or to the familiar epidermoid carcinoma

To allow the argument to be continued it will be taken as agreed that the spectrum consists of various forms of neoplasia of the primitive mesenchyme, some of which are indistinguishable from undifferentiated tumours of immature epithelial character, and of some growths sufficiently differentiated to have characters easily recognised in histological section Outstanding among these conditions is the familiar Hodgkin's disease, but Brill-Symmer's disease also has an individual appearance Both of these conditions are true reticuloses in the sense that they appear as systemic diseases affecting the lymphoreticular tissues, but can be equally correctly described as tumours of the primitive mesenchyme A third reticulosis which has recently been described in detail is the lipoid reticular form with three variants, eosinophil granuloma, Schuller-Christian disease and the Letterer Siwe syndrome A few cases of this reticulosis have been treated by us but not enough for separate classification and useful comment This may not be the last of the reticuloses to be distinguished, but if new forms await discovery they must be very rare.

My second main group includes all the lymphoreticular sarcomas and anaplastic tumours because I believe that, although lymphosarcoma and reticulum cell sarcoma are sufficiently differentiated to be recognised, they merge imperceptibly into the anaplastic tumours Outside our spectrum but very close to it come the cancers described as anaplastic, lympho-epithelioma and transitional cell carcinoma, none of which can be excluded when the anaplastic sarcomas are studied It may seem that all this discussion has merely separated out Hodgkin's disease, a highly individual condition often diagnosed by clinical examination, and leaves all the other lymphoreticular tumours in a state of complete confusion There is confusion, but that is why it is necessary to search for facts on which treatment may be based, and I believe that when the analysis of our findings has been followed it will be agreed that this simple division into two groups allows treatment to be determined

The acceptance of the theory of mesenchymal origin does not solve all the problems of the diagnosis and treatment of these puzzling diseases There are some strange anomalies in their behaviour, and they have not yet been satisfactorily separated from the infective granulomas There is, for instance, continuing confusion about the nature of the condition known as sarcoidosis Thanks to the work of Cameron and Dawson we now recognise this as a form of tuberculosis, but in the U S A it is often described as if it were a true neoplasm There are considerable differences between the work published abroad and that published in this country, and it sometimes seems that the same name is not given to the same disease

MATERIAL

The material available for analysis is provided by the cases treated at the Christie Hospital, Manchester, during the eight years 1940 to 1947 on a diagnosis of " reticulo-endothelial neoplasia," a term adopted by us in 1937 and much used by radiotherapists but unpopular with pathologists, who now replace it by lymphoreticular neoplasia Nearly 900 cases were so listed, but of these I have discarded —

1 Sixteen bone tumours (Ewing's tumours and multiple myelomatosis)
2 Thirteen cases of polycythæmia (number too small for analysis)
3 Ninety-four cases classed as reticulo-endothelial neoplasia but lacking definite pathological report

I was tempted to use those cases without pathological report which followed a characteristic clinical course but decided against this in case they might invalidate my comparisons The cases to be analysed, 777 in all, were without exception proved by pathological examination of sections The diagnosis was not always immediate, but the case records were often in themselves complete confirmation of a report which had expressed some doubt Sometimes clinical findings alone were enough, but further biopsies were often taken, sometimes before instituting further treatment or because reponse was unexpected There were also a number of autopsies

The method of taking the biopsy is important The small amount of tissue made available by aspiration or even by the new drill biopsy instruments is inadèquate for the diagnosis of these border-line conditions If possible a whole lymph node should be excised or, in cases where the nodes are fixed in a large mass of tumour, a substantial piece should be taken On the other hand we have found that attempt at complete excision, except in really early cases where block dissection could be carried out, was followed by early and widespread metastases Good biopsies having been available, it is possible to claim that the classification now to be given is based on pathology, and even a report of anaplastic tumour was acceptable, particularly as it was often possible to get an expression of opinion regarding probable origin by discussing the case with the reporting pathologist

The cases are grouped as follows —

Hodgkin's disease	275 cases
Brill-Symmer's diseases	24 ,,
Lymphosarcoma	108 cases
Reticulum cell sarcoma	57 ,,
Anaplastic tumours, may be either sarcoma or carcinoma	156 ,,
The leukæmias	157 ,,

The two conditions which may be regarded as true reticulosis have been grouped together because of the similarity of their multifocal lymphadenopathy and systemic symptoms Both must be regarded as almost incurable although their course may be long, sometimes lasting for years, the long duration showing as five-year survivals in the tables of results Occasionally an early case radically treated either by surgery or by irradiation seems to be cured, but this is rare because, even if the treated lesion remains well, new manifestations finally appear, although they may take forms so unexpected that they are not at first recognised Hodgkin's disease is the commonest of all these neoplasias, and its histology has often been described Jackson [4] and Parker have published a detailed study in which they subdivide into three groups Hodgkin's paragranuloma, Hodgkin's granuloma, and Hodgkin's sarcoma Their description is that the paragranuloma is found in lymph nodes with lymphoctytes as the predominant cell, although Reed-Sternberg cells are found on searching There are transition forms to the granuloma which is usually widespread and characterised by the presence of many Reed-Sternberg cells and by pleomorphism The sarcoma usually originates in the intra- or retro-peritoneal lymph nodes or abdominal organs and behaves as a malignant infiltrating tumour The diagnosis of Hodgkin's disease is established by the presence of Reed-Sternberg cells It has not been possible to divide the Manchester material into these three types There have been a number of cases diagnosed as " early Hodgkin's " which fit with the histological picture of the paragranuloma, but the diagnosis is made on small nodes removed for biopsy, and such a report may be received even when there are advanced lesions elsewhere in the body Nor has it been possible to distinguish sarcomas of the type they describe There have been true sarcomas infiltrating outside the capsule of the lymph nodes and producing secondary deposits in lung, liver or bone, but they have not been common within the abdomen In general, the only consistent histological difference we have found to distinguish early and late cases has been the number of mitoses indicating rate of growth The points on which the diagnosis rests are the characteristic Reed-Sternberg cells, the endothelial reaction, the position of the cells in the medulla and the presence of eosinophils, fibrosis and necrosis

Clinical characters are a low average age incidence, preponderance of males and a comparatively long duration before the need for treatment is realised This is probably because the first sign is nearly always painless enlargement of lymph nodes causing no inconvenience Hodgkin's disease is essentially a neoplasm of lymph nodes which, unless sarcoma supervenes, remain freely mobile and have a characteristic rubbery feel Systemic complications, fever, itching of the skin and anæmia are common and may lead to profound cachexia and death The other cause of death is the appearance of sarcomatous infiltration and metastatic deposits The nature of this sarcomatous change is interesting and it is used as an argument in favour of true neoplasia against the theory of a specific infection On the other hand, it is important that this is the only disease in this series which consistently shows a response to treatment by nitrogen mustard There is, of course, an effect in the blood diseases, but this is due to the generalised action of these drugs on the hæmopoietic system In Hodgkin's disease it has a specific effect which we have not seen in Brill-Symmer's, or any of the sarcomas Such specificity cannot help but suggest an important difference in ætiology and development, but at present it can only be said that the question of the exact nature of all the reticuloses remains open

FIG A1 —Lymph node showing typical Hodgkin's disease
FIG A2 —The same to show Reed Sternberg cells
Fig A3 —Histological picture in Brill Symmer's disease
FIG A4 —Lymph node showing typical lymphosarcoma
FIG A5 —The same to show mitoses
FIG A6 —Anaplastic tumour of tonsil secondary in cervical lymph node Reported as "probably epithelial"
FIG A7 —The same to show epithelial type of cell

Brill-Symmer's Disease, also called lympho or giant follicular reticulosis, has a characteristic histological appearance The huge follicles are packed with lymphocytes with a topography quite different from that of lymphosarcoma Clinical characters are variable, age incidence is high, there is a slight preponderance of females in our small series, and duration is even longer than in Hodgkin's disease It is also a reticulosis, the first sign being enlargement of lymph nodes where it usually grows slowly causing little or no disturbance and is sometimes reported as a benign condition At a later stage, and this may supervene without obvious early signs, it causes generalised and sometimes enormous enlargement of lymphoid tissue throughout the body with extensive œdema and serous effusions It kills by pressure from the masses of tumour, anæmia and cachexia or by sarcomatous transformation The average course is longer than that of Hodgkin's disease

Lymphosarcoma may be regarded as a true sarcoma arising in primitive mesenchyme and differentiating to the production of lymphocytes The second tumour in this group, the reticulum cell

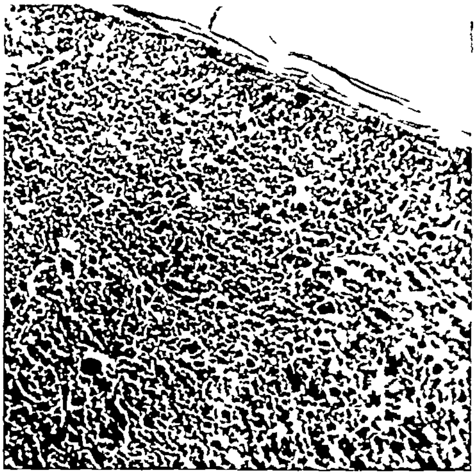

Fig A1

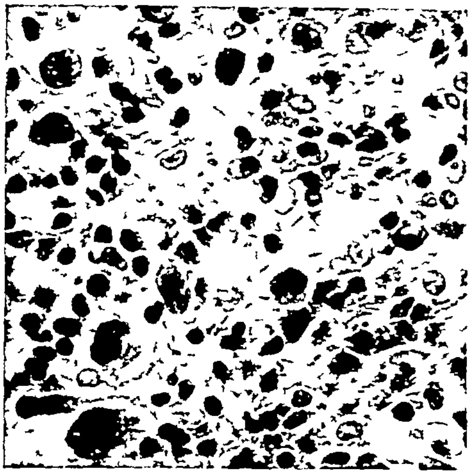

Fig A2

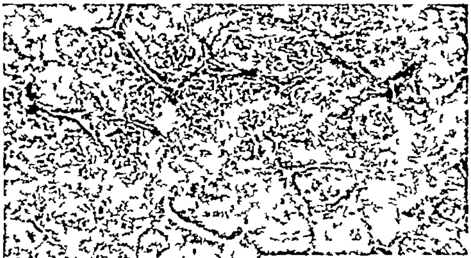

Fig A3

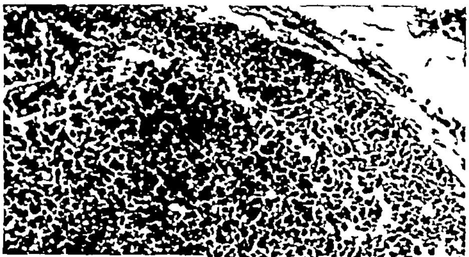

Fig A4

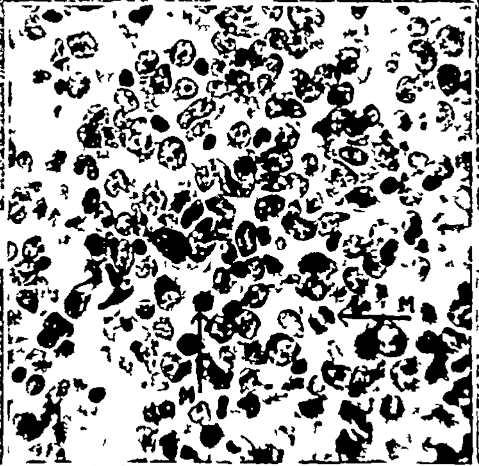

Fig A5

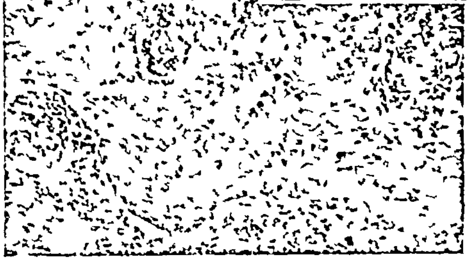

Fig A6

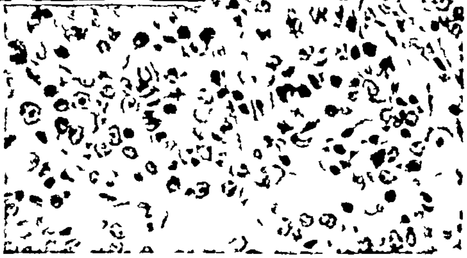

Fig A7

sarcoma, merely shows differentiation towards another type, the reticulocyte The clinical characters of the two sarcomas are similar The age incidence is higher and males are less predominant than in Hodgkin's Duration is comparatively short Both tumours behave as infiltrating sarcomas, but there may be an apparently multifocal origin in lymph nodes, suggesting kinship with the reticulosis Lymphosarcoma is the only neoplasm in the series showing a tendency to develop leukæmia, and sections of lymph nodes from the two conditions are much alike

Anaplastic Tumours—Under this heading are collected all the tumours with pathological reports expressing doubt as to whether they were sarcoma or carcinoma, including the description " lympho-epithelioma " Here are some typical reports —

> " An anaplastic tumour, I do not know whether it is sarcoma or carcinoma, but I think it is reticulum cell sarcoma "
> " I think this is an epithelial tumour, but I cannot be sure "
> " Malignant cells infiltrating lymphoid tissue, carcinoma, I think "

Clinically the characters of these tumours are almost indistinguishable from those of the more differentiated sarcomas with which they are grouped, except that they are almost entirely confined to the lymphoid tissues of the head and neck Metastases from them may be found in any organ or tissue Such a report from axillary or supraclavicular nodes suggests the presence of a primary anaplastic tumour in the lung

The Leukæmias must also be accepted as reticuloses, and polycythæmia is only omitted because the number of our cases is too small for useful analysis The blood picture and clinical features are so well known that no description is needed Diagnostic difficulties may be encountered when multiple enlargement of lymph nodes is combined with a moderately raised white count, but the high proportion of lymphocytes in the circulating blood usually answers doubts and confirms the presence of leukæmia The atypical signs of aleukæmic leukæmia may be more confusing The peripheral blood picture may appear normal although other signs of a reticulosis are present, and it is only when the rapid progress of the disease, in spite of apparently appropriate treatment, raises alarm that a marrow smear provides the diagnosis

ANALYSIS OF MATERIAL

A point has now been reached when, leaving the blood diseases aside, attention can be focused on the two main groups, one containing the two reticuloses, Hodgkin's and Brill-Symmer's diseases, the other the lymphoreticular sarcomas and the anaplastic tumours which may be either sarcomas or tumours derived from primitive epithelial tissue The knowledge that there are rare variants and transitional forms allows the inclusion of all forms of neoplasia showing similarity of appearance and behaviour, even if this sometimes leads to mistakes in classification It seems, for instance, that there will be a few reticuloses lacking histological character overlapping into the group of sarcomas, and on the other hand some squamous cell carcinomas anaplastic at the point from which a biopsy was taken The tables which follow have been prepared to show certain similarities and contrasts in support of my thesis that this grouping is reasonable and helpful The first table compares Hodgkin's and Brill-Symmer's with the age incidence, sex and duration of the disease before the patient came for treatment This is a table of contrasts and is an argument in favour of the two being distinct and individual conditions This table shows the proportion of patients with disease present in certain sites whether it was present when the patient was first seen or appeared later There is a real similarity between the two conditions, both being diseases of the lymph nodes In Hodgkin's the first site affected was usually the cervical nodes, and spread to mediastinal and hilar nodes was common Brill-Symmer's disease often presented in the groin,

TABLE I

Distribution by Age, Sex and Duration of Symptoms—Hodgkin's and Brill-Symmer's Disease 1940-1957

Pathological Report	Number Treated	Age Groups				Per cent Males	Duration of Symptoms (months)			
		Under 21	21 40	41 60	Over 60		Under 3	3 6	6 12	Over 12
		Per cent	Per cent	Per cent	Per cent	Per cent	Per cent	Per cent.	Per cent	Per cent
Hodgkin's disease	275	20	45	30	5	69	15	19	23	43
Brill Symmer's disease	24	0	29	54	17	46	0	8	46	46

TABLE II

Principal Sites known to have been Involved by Disease—Hodgkin's and Brill-Symmer's Disease 1940-47

Pathological Report	Number Treated	Superficial Nodes Neck Axilla and Groin	Mediastinum and Lung	Nodes Abdomen	Spleen
		Per cent	Per cent	Per cent	Per cent
Hodgkin's Disease	275	100	50	42	20
Brill Symmer's Disease	24	100	17	62	37

TABLE III

Complications—Hodgkin's and Brill-Symmer's Disease 1940 47

Pathological Report	Number Treated	Early Fever	Early Anæmia	Itching	Serous Effusion
		Per cent	Per cent	Per cent	Per cent
Hodgkin's Disease	275	32	35	10	8
Brill Symmer's Disease	24	0	25	0	33

spreading to iliac and retroperitoneal nodes This accounts for the slight difference in incidence for these sites The complications of fever and anaemia are described as "early" to indicate that they were present when the patient was first admitted to hospital In the terminal stages of disease they become almost universal Comparison of these complications suggests the presence of two members of one family developing in different directions With Table IV a new comparison begins, that of the partly differentiated lymphoreticular sarcomas and the anaplastic tumours The two sarcomas being exactly the same are shown together and in contrast with the anaplastic tumours but, even so, there are no important differences in age or sex It is only under duration that a significant difference appears, the shorter interval before anaplastic tumours attracts attention This table separates the differentiated sarcomas and shows slight but significant differences between lymphosarcoma and anaplastic tumours with reticulum cell sarcoma, sometimes like lymphosarcoma and sometimes bridging the gap between them Lymphosarcoma has some characters

TABLE IV

Distribution by Age, Sex and Duration of Symptoms—Lymphoreticular Sarcomas and Anaplastic Tumours 1940 47

Pathological Report	Number Treated	Age Groups				Per cent Males	Duration of Symptoms (months)			
		Under 21	21 40	41 60	Over 60		Under 3	3 6	6 12	Over 12
Lymphoreticular sarcomas	165	Per cent. 12	Per cent 22	Per cent. 41	Per cent. 25	Per cent. 57	Per cent. 28	Per cent. 24	Per cent. 22	Per cent 26
Anaplastic tumours										
More like carcinoma	56	2	30	45	23	54	29	29	29	14
More like sarcoma	100	10	13	38	39	66	37	33	24	6
Total anaplastic tumours	156	7	19	40	33	62	34	31	26	9

TABLE V

Principal Sites known to have been Involved by Disease—Lymphosarcoma, Reticulum Cell Sarcoma and Anaplastic Tumours 1940 47

Pathological Report	Number Treated	Pharynx and Naso pharynx	Nodes Neck	Nodes Axilla and Groin	Nodes Mediastinum and Abdomen	Metastinum Liver Lung Bone.
		Per cent	Per cent.	Per cent	Per cent.	Per cent.
Lymphosarcoma	108	24	70	82	50	18
Reticulum Cell Sarcoma	57	26	70	44	45	45
Anaplastic Tumours either Sarcoma or Carcinoma	156	63	86	18	25	52

like those of the first group and some cases with this diagnosis behave like reticuloses The possibility that some of these cases were lymphatic leukæmias of slow onset has been mentioned, and it may be worth remembering that during the first half of the period under review Brill-Symmer's disease was not so well known Included in the group of cases of the reticuloses are one or two first referred to us as lymphosarcoma, and it is likely that there were some others never correctly diagnosed Even if the total number of incorrect diagnoses was small they could make a perceptible difference in the percentages This table again shows a sub-analysis of the group of anaplastic tumours There is only one difference worth noting—the low incidence of involvement of nodes other than cervical nodes in tumours which may be carcinomas None of the differences are statistically significant and no reason is found for separating this group into two sections

TABLE VI

Principal Sites known to have been Involved by Disease—Sub-Analysis of Anaplastic Tumours 1940-47

Pathological Report	Number Treated	Pharynx and Naso-pharynx	Nodes Neck	Nodes Axilla and Groin	Nodes Mediastinum and Abdomen	Metasinum Liver Lung, Bone
		Per cent	Per cent	Per cent	Per cent	Per cent
More like sarcoma	100	59	87	23	33	38
More like carcinoma	56	70	96	9	19	49

TABLE VII

Distribution by Age, Sex and Duration of Symptoms—Hodgkin's Disease, Lymphoreticular Sarcomas and Anaplastic Tumours 1940-47

Pathological Report	Number Treated	Age Groups				Per cent Males	Duration of Symptoms (months)			
		Under 21	21 40	41 60	Over 60		Under 3	3 6	6 12	Over 12
		Per cent	Per cent	Per cent	Per cent	Per cent	Per cent	Per cent	Per cent.	Per cent.
Hodgkin's disease	275	20	45	30	5	69	15	19	23	43
Lymphoreticular sarcomas and anaplastic tumours	321	10	20	41	29	59	31	27	24	18

I believe that the three preceding tables show enough similarity to allow the lymphoreticular and anaplastic tumours to be regarded as a single group for comparison with Hodgkin's disease Brill-Symmer's is omitted because of the small number of cases In Table VII the figures are of an order to make all the differences shown significant There is thus no doubt as to the importance of the differences except that there is an overall preponderance of males Table VIII shows significant differences for incidence in every site except for metastases in lung, liver and bone Such metastases are nearly always a terminal sign In the sarcomas they appeared as a rule within two years of treatment, or in generalised cases were present when the patient sought treatment and were the cause of early death In Hodgkin's disease they usually appear in the later stages of a long illness, so that the apparent similarity is less obvious clinically This table should be compared with Table V which shows the sites of involvement in the second group A comparison of the incidence of complications again shows important differences between the two groups

TABLE VIII

Principal Sites known to have been Involved by Disease—Hodgkin's Disease, Lymphoreticular Sarcomas and Anaplastic Tumours 1940 47

Pathological Report	Number Treated	Pharynx Nasopharynx	Nodes. Neck	Nodes Mediastinum and Abdomen	Other Nodes	Spleen	Metastinum Liver Lung Bone
		Per cent.	Per cent	Per cent.	Per cent.	Per cent.	Per cent.
Hodgkin's disease	275	0 4	90	82	58	20	37
Lymphoreticular sarcomas and anaplastic tumours	321	45	75	35	43	6	35

TABLE IX

Complications—Hodgkin's Disease, Lymphoreticular Sarcomas and Anaplastic Tumours 1940-47

Pathological Report.	Number Treated	Fever	Itching	Serous Effusion	Anæmia.
		Per cent	Per cent.	Per cent.	Per cent.
Hodgkin's Disease	275	32	10	8	35
Lymphoreticular sarcomas and anaplastic tumours	321	0	0	2	9

Discussion of Tables

I have now taken two conditions, Hodgkin's disease and Brill-Symmer's disease, so distinct in character that they can be easily recognised, but showing a family resemblance strong enough to prove a relationship, and have compared them with three tumours of varying histological type, brought together as another family whose ancestry is the same but whose development is different The members of the first family are reticuloses affecting lymph nodes and only involving other tissues and organs at a late stage of the disease Their systemic manifestations play an important part in prognosis The second family consists of malignant tumours arising in, or in association with, lymphoreticular tissue infiltrating locally and producing secondary deposits in lymph nodes and distant metastases Between the two families are some of the transition forms mentioned by Willis, and in the second family are found some atypical members which may be intruders from another family altogether, the carcinomas This does not alter the fact that it is now possible to separate this apparently heterogeneous collection of neoplasms into two main groups One of these consists of lymphoreticular disease multifocal in origin in the sense that all lymphoreticular tissue in the body either simultaneously, or in an order which cannot be predicted, responds to an unidentified stimulus by hyperplasia going on to neoplasia The other consists of a group of malignant tumours mainly lymphoreticular sarcomas but including some completely anaplastic growths, unifocal in the sense that there is a primary tumour which gives rise in the ordinary way to secondary deposits in lymph nodes and distant metastases If this essential contrast is accepted it is not surprising that the groups call for different treatment and respond differently to treatment given

METHODS OF TREATMENT

Before discussing methods of treatment it is important to find some way of assessing the degree of advancement of the cases forming the sample treated Where malignant disease is concerned the idea of staging is familiar For the forms of neoplasis now in question there is only one division, but a division of such importance that treatment is almost entirely determined by it This division is into localised and generalised disease and is applicable to all lymphoreticular neoplasia of both groups The nature of these diseases with their tendency to multifocal manifestations makes it necessary to define what is meant by a localised lesion Our definition of a localised lesion is that the neoplasia is, as far as can be ascertained, confined to one region of the body This is meaningless until the regions are themselves defined, and it must be admitted that our regions are not those of the anatomist They are best described as parts of the body which can be conveniently treated by X-rays to a dose believed to be capable of producing complete and permanent resolution of sensitive tumours These regions are —head and neck to the level of the clavicles, the mediastinum, each axilla and each groin The abdomen can also be regarded as a region if only lymph nodes are involved The disease is regarded as generalised when two or more of these regions are involved, or when in addition to regional nodes organs such as spleen, liver, lung or bones are the site of tumour formation

At this point I should like to say that I confine my discussion of treatment to X-ray therapy, which I still regard as by far the most important means of treating all these diseases In Manchester we divide our techniques into radical and palliative and usually make a deliberate choice of one or the other before beginning treatment In general, radical techniques are used for localised, and palliative techniques for generalised lymphoreticular tumours with the variations called for by difference in the sites affected and the age and general condition of the patient

THE TREATMENT OF HODGKIN'S AND BRILL-SYMMER'S DISEASES

It has been agreed that both these diseases are by their nature generalised reticuloses, but it often happens that the first sign is enlargement of one group of lymph nodes, possibly a single lymph node The patient seldom seeks advice before signs of new growth in the nodes are obvious and may wait till several groups of nodes have grown to a large size , even so, about one-third of the patients come for treatment with the disease still confined to a single region and thus, by our definition, localised In spite of the probability that as they are true reticuloses new foci will soon appear in other sites there may be a long interval before extension occurs, and radical treatment should be tried It has been claimed that surgical dissection of the affected nodes may cure the early case We believe that radiotherapy to sufficient dosage may be equally effective In certain selected cases, therefore, the radical methods to be described for the treatment of the radio-sensitive sarcomas are appropriate for early Hodgkin's or Brill-Symmer's disease

Unfortunately, it is more usual to be faced with the problem of a generalised reticulosis There are several groups of enlarged lymph nodes and possibly such signs of failing health as fever with night sweats and a falling red blood count Treatment must then be palliative We use two X-ray techniques, a chasing technique and a low dose palliative technique of regional type The first is preferred when there are several foci of disease and treats each focus separately, using fields which cover the lesion but without a wide margin, and gives a dose high enough to produce at least temporary disappearance while avoiding severe reactions This technique conserves tolerance by treating only a small volume of tissue but to dosage likely to be biologically efficient within the volume irradiated The tolerance will be needed for the treatment of the new manifestations which will continue to appear until finally they can no longer be controlled

TREATMENT OF THE LYMPHORETICULAR SARCOMAS

The tumours in my second group are more often treated while they are still localised, possibly because tumours of the pharynx and nasopharynx, where they tend to be located, inconvenience the patient and he consults his doctor within a comparatively short time In the treatment of localised lymphoreticular neoplasia, and this applies also to the first group, the guiding principle is that it is necessary to include not only the visible or palpable tumour but also the group of lymph nodes reached by the lymphatics draining the area and any probable line of extension, for instance, the foramina at the base of the skull if the tumour is in the nasopharynx This means that the fields must be very large A frequent arrangement uses four fields to cover the whole head and neck from a line above the base of the skull to below the clavicles or neck and mediastinum (Fig B10) The axilla and groin are easier to treat, but even there the homolateral supraclavicular nodes or entire iliac fossa must be included When treatments of this order are under consideration it is necessary to balance the volume of tissue to be treated against the dose which can be tolerated The questions of local tolerance of skin, mucous membrane and connective tissue have been much discussed and are fairly well understood, but here we are dealing with something more than local tolerance and in many cases a considerable systemic effect must be expected In the treatment of the head and neck severe reactions are produced in the mouth and throat Taste and smell may be lost and the secretion of the salivary glands is reduced so that it becomes difficult to maintain nutrition If part of the abdomen is included, any irradiated viscera will react and both bowel and kidney are radiosensitive organs In addition the radiation of large sensitive tumours must result in the breaking down of their constituent cells with liberation of toxic products which must be excreted The general tolerance of the patient is thus under considerable strain and the dose to be given is determined by the sum of the local and general effects These effects are, however, temporary and are not too heavy a price to pay for the chance of cure

TABLE X

Clinical Features of Three Types of Leukæmia 1940-47

Pathological Report	Number Treated	Nodes Neck	Other Nodes	Spleen	Early Anæmia
		Per cent	Per cent	Per cent	Per cent.
Myeloid	64	0	0	100	81
Lymphatic	57	74	95	77	35
All acute and aleukæmic	36	70	78	75	100

When the lymphoreticular sarcomas are generalised it can be said that multiple metastases are present Cure is almost impossible, but good palliation can be obtained because of the radiosensitivity of these tumours The techniques used are those already described for the treatment of the generalised reticulosis, but they are less effective for the sarcomas because vital organs are invaded Post-mortem examinations on some of our cases showed nearly every organ in the body to contain secondary deposits

THE LEUKÆMIAS

Before the results of treatment are described this survey of the reticuloses is completed by two tables comparing the clinical findings in the leukæmias Again I have simplified the table by making only three groups, chronic myeloid leukæmia, chronic lymphatic leukæmia

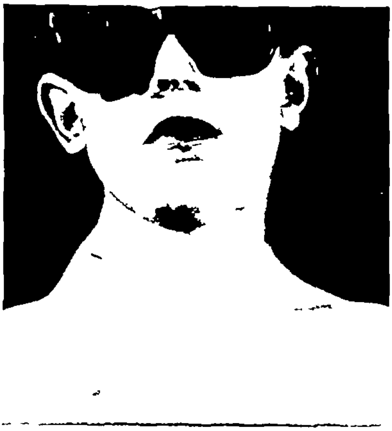

Fig B1 —Patient with Hodgkin's disease in cervical lymph nodes

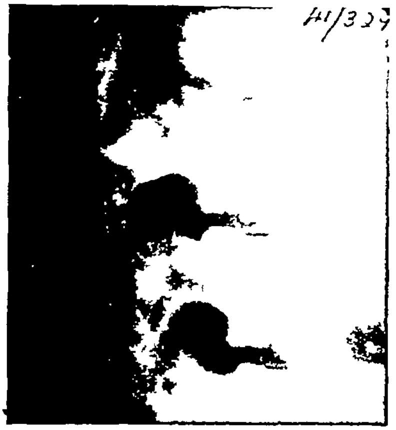

Fig B2 —Secondary deposits in body of vertebra in Hodgkin's disease

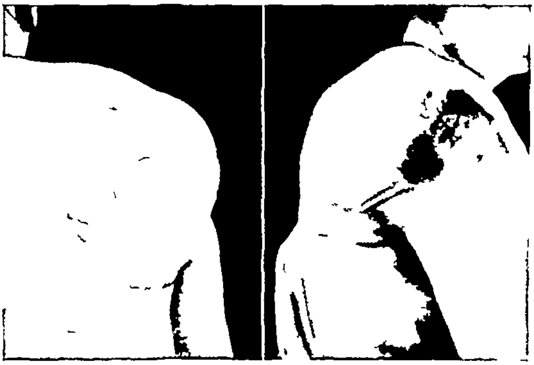

Fig B3 —Sarcomatous involvement of subcutaneous tissues and muscle in Brill Symmer's disease

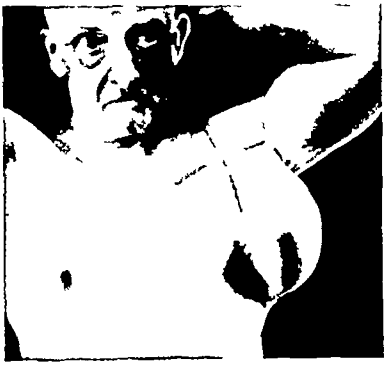

Fig B4 —Lymphosarcoma in axillary and supraclavicular lymph nodes

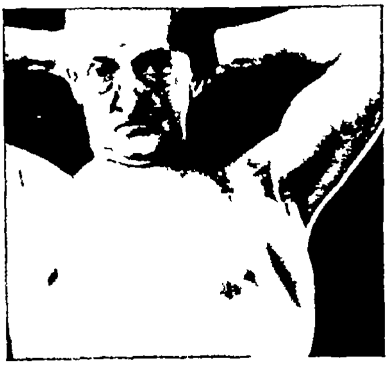

Fig B5 —The same one month after completing regional X ray therapy Central dose 3000 r

and all acute and aleukæmic types taken together, inaccurate but convenient as their prognosis is uniformly bad The three types are obviously completely different Myeloid leukæmia shows the characteristic blood picture and enlargment of the spleen , lymphatic leukæmia effects the production of lymphocytes in nodes as well as marrow, but enlargment of the spleen and anæmia are less common, at least in the earlier stages Acute leukæmia affects every part of the hæmopœtic system, and up till now has proved almost completely resistant to all forms of treatment This is a comparison between lymphatic leukæmia and lymphosarcoma to bring out the similarity which has already been mentioned The differences are seen in the percentages of cases with enlargement of the spleen, and with leukæmia present

TABLE XI

Clinical Features of Lymphosarcoma and Lymphatic Leukæmia 1940 47

Pathological Report	Number Treated	Neck Nodes Involved	Other Nodes Involved	Spleen	Anæmia	Leukæmia
		Per cent	Per cent	Per cent	Per cent	Per cent
Lymphosarcoma	108	70	82	14	18	100
Lymphatic leukæmia	57	74	95	77	35	8

TABLE XII

Radiotherapy Results of Localised Hodgkin's Disease, Lymphoreticular Sarcomas and Anaplastic Tumours

Pathological Report.	Number Treated	1940-1945					
		Alive 3 Years		Alive 5 Years		Well 5 Years	
		Number	Crude Rate	Number	Crude Rate	Number	Crude Rate.
			Per cent		Per cent.		Per cent.
odgkin's disease	42	29	69	23	55	10	24
ymphoreticular sarcomas and anaplastic tumours	115	71	62	59	51	55	48

The leukæmias recorded here were all treated in one of two ways, either by X-ray therapy to the spleen or by chemotherapy using urethane The second method was only used towards the end of the period and seldom as the only therapy, X-ray having played some part, so when the results are given the two methods cannot be separated

Results of Treatment

The figures given are all crude survival rates showing the percentage of the patients treated alive at a chosen anniversary, in this case the third and the fifth Patients reported as " well " had no sign of disease when examined for the record and had needed no further treatment after the first course This table compares the results obtained in localised Hodgkin's disease with those of the lymphoreticular sarcomas at three and five years There is little difference in the survival rates but in the last column the proportion of cases recorded as "well" shows that long survival in Hodgkin's disease is often associated with slow extension and long remission after treatment whereas the sarcomas, unless metastases appear, may be permanently controlled A number of ten year survivals among the earlier cases of sarcoma show that this is possible

TABLE XIII

Radiotherapy Results of Generalised Hodgkin's Disease, Lymphoreticular Sarcomas and Anaplastic Tumours

Pathological Report	Number Treated	1940 1945					
		Alive 3 Years		Alive 5 Years		Well 5 Years	
		Number	Crude Rate	Number	Crude Rate	Number	Crude Rate
			Per cent		Per cent		Per cent
Hodgkin's disease	109	25	23	12	11	2	2
Lymphoreticular sarcomas and anaplastic tumours	77	14	18	5	6	3	4

Although histology is the determining factor there are others which also influence prognosis Tumours confined to the head and neck have a good prognosis, in spite of the fact that some of them may be more resistant carcinomas, and should be given full treatment even if a large tumour is accompanied by bilateral enlargement of lymph nodes Prognosis is also good when the disease is confined to a single group of superficial lymph nodes, but such limitation is rare

TABLE XIV

Radiotherapy Results—All Cases Hodgkin's Disease, Lymphoreticular Sarcomas and Anaplastic Tumours

Pathological Report	Number Treated	1940 1947		Number Treated	1940 1945	
		Alive 3 Years			Alive 5 Years	
		Number	Crude Rate		Number	Crude Rate
			Per cent			Per cent
Hodgkin's disease	275	85	31	151	32	21
Lymphoreticular sarcomas and anaplastic tumours	321	128	40	192	69	36

I have no survival figures at five years for Brill-Symmer's disease because only 3 cases with this diagnosis were treated more than three years ago At the third anniversary 8 of the 24 cases, none of which was localised, were alive Only one was well The generalised cases of Hodgkin's disease and of lymphoreticular sarcoma show an equally bad prognosis

The results for all cases, localised and generalised combined, are given in this table in which are shown the three year results of all cases treated up to 1947 assessed at the third anniversary They still show a significant advantage for the sensitive sarcomas, using this term to include all the malignant tumours of the second group The generalised sarcomas are a smaller proportion of the whole but they are so rapidly fatal that they depress the survival curve of the sarcomas This curve is contrasted with that of Hodgkin's disease on a graph To complete this presentation of results the next table shows those obtained in the treatment of the three forms of leukæmia There is little difference between the prognosis of the chronic forms That of the acute forms is so bad that not one of these cases survived for one year The last table compares the results in Hodgkin's disease and the leukæmias

Comparison of survival rates in Hodgkin's disease and lymphoreticular sarcoma.

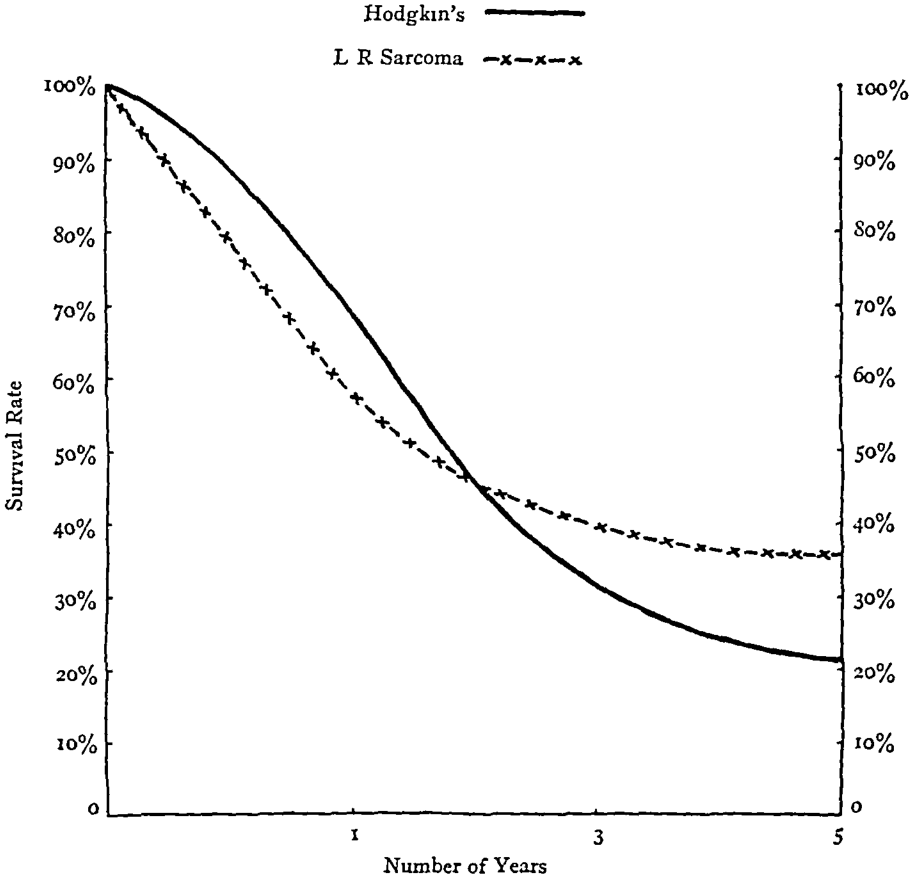

FIG C —Five year survival curve for Hodgkin's disease and lymphoreticular sarcoma

Those in leukæmia are the worse of the two, and this is even more obvious at five years when the survival of leukæmia falls to 3 per cent

FINAL DISCUSSION

It may seem to you that I am merely restating the obvious when I draw your attention to the great difference in prognosis which appears as soon as these diseases become generalised The prognosis for localised sarcoma, even of a most malignant type, is as good as that of squamous cell cancer in the mouth with no involvement of lymph nodes, yet the staging of sensitive sarcomas includes bilateral involvement of the cervical nodes in the localised group The prognosis of the true reticuloses, even when localised, is less good, and that of all generalised lymphoreticular neoplasia is frankly bad It is true that all malignant disease is much less likely to be cured once it has spread beyond the primary site, so why should anything different be expected of the lymphoreticular tumours ? There is, however, a difference These tumours are radio-sensitive and do not need very high doses to ensure complete disappearance, so that many attempts have been made to achieve this by treating all sites of neoplasia, including irradiation of the whole trunk Unfortunately, success has not been obtained

TABLE XV

Treatment Results of Leukæmias

Pathological Report	Number Treated	1940 1947	
		Alive 3 Years	
		Number	Crude Rate
			Per cent
Myeloid	64	19	30
Lymphatic	57	14	25
Acute and aleukæmic	36	0	0

TABLE XVI

Treatment Results—Hodgkin's Disease and Leukæmia

Pathological Report	Number Treated	1940 1945	
		Alive 3 Years	
		Number	Crude Rate
			Per cent
Hodgkin's disease	275	85	31
Leukæmias	157	33	21

because even with the most radio-sensitive of the tumours the general tolerance of the patient is scarcely ever good enough to allow the necessary dosage to be delivered to all foci of disease either by treating all at once or by treating them in rapid succession

The question of the combination of local and general tolerance which allows the successful treatment of one of our regions has already been discussed The tolerance needed for the treatment of generalised disease is that of the individual as a whole There are two main reactions of systemic intolerance, one immediate, radiation sickness, and one delayed, changes in the blood picture due to destruction of stem cells in the marrow and of sensitive cells in the circulating blood The first of these reactions can to a great extent be avoided by careful gradation of dosage, beginning with a small daily dose and increasing to the desired level with careful attention to effect and is not, in my experience, a frequent cause of failure The limiting factor which makes it impossible to give curative doses of very large volumes is the inclusion of too much of the blood-forming marrow Effect on marrow is reflected by changes in the circulating blood All elements are diminished, white cells, platelets, and to a lesser degree red cells, and the degree of change is related to the normal life of the cell in the blood stream and the speed of replacement The first cells to show a decrease in the number circulating are the lymphocytes, then the leuocytes, the platelets and, finally, the erythrocytes It is probable that when large volumes, for instance 25 per cent of the tissues of the body, are irradiated these decreases are proportional to the doses given provided that other factors are constant I am not concerned here with the results of whole body radiation to single high doses such as may occur with atomic bombing but with the effect on hæmopoiesis of doses of the order needed to secure resolution of sensitive tumours Experience has shown that at least half the trunk can be irradiated to the necessary dose level if suitable fractionation is used The total white count of peripheral blood will fall to a low level with the lymphocytes leading and indicating the speed of total drop We regard a count of 2000 total white cells as an indicator of risk, but when the clinical condition was good we have taken our white counts as low as 1000 total whites with no permanent ill effects After the appearance of the leucopenia, the platelet count also falls, and there is little doubt that there is not only damage to the megakaryocytes but also to the whole erythropoietic series in the marrow If the proportion of blood-forming marrow which is irradiated is not too big, hypertrophy outside the irradiated volume maintains the necessary replacement, and in time recovery takes place The failure of erythropoiesis is, therefore, masked because the long life of the red cell in the circulation gives time for hypertrophy and recovery When the damage has been spread over more of the marrow enough may not be spared to allow hypertrophy to meet the need for replacement, and partial recovery will not be enough to prevent the appearance of anæmia Severe injury may result in complete aplasia of all elements in the treated marrow with death from aplastic anæmia unless the patient dies at an earlier stage from infection It is, of course, not only in the terminal stages that infection is a danger but throughout the period while the counts are low A low leucocyte count interferes with the normal mechanism of defence but does not altogether prevent the usual response Lymphocytopenia may be almost more important because the lack of lymphocytes results in loss of the antibodies normally produced by them All these effects can be obtained by the irradiation of the normal individual When the marrow is already the site of disease, as in the reticuloses, and the patient is suffering from fever, septic ulceration or malnutrition, the dangers are much greater It seems, then, that the attempt to irradiate all foci of generalised disease must be renounced We tried to overcome the difficulties by irradiating the whole trunk in strips each of which in turn received a dose which we hoped might prove to be biologically effective but we were not successful, and I do not believe that the various forms of whole body radiation described as teleroentgen therapy can claim any strikingly good results Must we then admit that there is no hope for the many patients suffering from generalised lymphoreticular neoplasia? I fear we must, if complete and permanent cure is in question The development of chemotherapy for these diseases is, therefore, very welcome, and further research is much needed The most important response so far has been that of Hodgkin's disease to the nitrogen mustards In some cases almost complete remission is obtained and lasts for many months, in others, remissions are much shorter though transient improvement is nearly always found

In my opinion, useful though chemotherapy is, it should not be the first treatment used, because I believe that in the early stages while systemic symptoms are not severe, local lesions can be controlled by the chasing technique with practically no effect on hæmopoiesis even when several masses of lymph nodes have to be irradiated The undesirability of any treatment which seriously interferes with erythropoiesis has already been stressed and is as important for chemotherapy as it is for radiotherapy On the other hand there are many cases when the problem is one of acute discomfort from fever, sweating and itching, and nitrogen mustard then gives genuine relief

The drug, triethylenemelamine, belongs to the same group and can be taken by mouth The immediate effects are less disagreeable and it is proving useful not only for Hodgkin's disease but for the leukæmias Urethane also can be used for leukæmia and we prefer it to nitrogen mustard for this purpose Various other drugs are now on trial, and may improve on any results so far obtained At present, however, a drug has yet to be found without a damaging effect on the marrow cells which must limit its use

Before finishing, the use of radioactive isotopes must be mentioned, but so far their role in the treatment of the lymphoreticular neoplasms has been unsatisfactory Radioactive phosphorus has a place, though no more important than that of X-rays in the treatment of leukæmia, but it has been tried with little success for the other reticuloses, and now few advocate further trial The possibility of finding a substance into which a suitable radioactive isotope could be inserted for differential absorption, analogous to that of iodine in the thyroid, maintains the hope that some day radio-sensitive tumours may be destroyed by radioactivity from within

CONCLUSIONS

1 All localised tumours with pathological reports suggesting that they may be lymphoreticular sarcoma should be treated by regional X-ray therapy to full dosage This can save at least 40 per cent of localised cases

2 The treatment of generalised lymphoreticular tumours, true reticuloses and sarcoma should be in the first place by palliative X-ray therapy which should aim at conserving the general tolerance of the patient

3 Chemotherapy may be a useful adjunct but should be restricted to the later stages

4 A biopsy is essential when lymphoreticular neoplasia is suspected

REFERENCES

[1] DAWSON, E K, INNES, J R M, and HARVEY, W F "Debatable Tumours in Human and Animal Pathology II Lymphosarcoma," *Edin Med Journ*, 54, 645
[2] WILLIS, R A (1948) "Pathology of Tumours," London
[3] DAWSON, E K, HARVEY, W F, and INNES, J R M, "Debatable Tumours in Human and Animal Pathology I Lymphœpithelioma," *Edin Med Journ*, N S IV, 44, 549
[4] JACKSON, H, and PARKER, F (1947), "Hodgkin's Disease and Allied Disorders," Oxford University Press, New York

IRON ABSORPTION TESTS IN ANÆMIA THE USE OF INTRAVENOUS IRON PREPARATIONS

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In recent years, following the work of Nissim (1947), who described a method of preparation of saccharated oxide of iron, there has been a revival of interest in the administration of iron preparations by the intravenous route

The use of saccharated oxide of iron has been described by Davidson and Girdwood (1948), Slack and Wilkinson (1949), Govan and Scott (1949), Sinclair and Duthie (1949, 1950) and others

The purpose of the present paper is to give an account of the response to intravenous iron in patients with iron deficiency anæmia who had failed to improve with prolonged courses of iron by mouth

In addition, since there was a possibility that the failure in response to oral therapy was due to malabsorption of iron, a test for iron absorption has been applied to many of these patients, to a series of control cases and to patients suffering from other forms of anæmia

Finally, in view of the importance of knowing to what extent iron administered intravenously is excreted, certain experiments have been carried out to measure the excretory capacity of the body for the metal

ABSORPTION OF IRON METHODS AND RESULTS

In all instances where the condition has been described as refractory, the patient had a prolonged period of treatment with oral iron preparations, including at least three weeks of this form of therapy in hospital

When it was sufficiently established that there was no response to iron by mouth, the patients were given intravenous injections of the preparation of saccharated oxide of iron marketed as "Ferrivenin" in divided doses to a total of from 1 to 1 8 gm.

Iron absorption curves were carried out on the lines suggested by Moore and Doan (1936) and Moore *et al* (1939) These workers showed that, following the ingestion of iron, there is a prompt rise in the serum iron level, apparent in the first half hour, reaching a maximum in two and a half to five hours, and gradually falling to approximately the basal level in twelve hours They concluded that although the test did not measure the total amount of iron absorbed, it did indicate the presence of absorption and gave some idea of its degree It was therefore felt that a test of this nature might be of value in demonstrating the presence or absence of iron absorption in these cases of hypochromic anæmia refractory to oral iron

On the day of the test, the patients' breakfast was restricted to a cup of tea and a piece of bread, since the taking of food is reputed to lower the serum iron content (Moore *et al*, 1939)

Blood samples were withdrawn before the ingestion of the test dose of iron and at two, four, six and sometimes twenty-four hours thereafter

In the early stages of the investigation, the patients were given 9 grains of ferrous sulphate (approximately 2 mgm per kilogram of body weight) as a test dose It was found, however, that the average rise of serum iron with this dosage was only 36 μg /100 ml of serum Since it had been demonstrated by Moore *et al* (1939) that over a twenty-four hour period the serum iron of patients on a mixed diet may show an hourly fluctuation of 35 μg /100 ml , it was decided to increase the test dose to 18 grains of ferrous sulphate

Unfortunately, however, certain cases had to be eliminated from the study because of nausea, vomiting or diarrhœa resulting from the administration of this larger dosage

Serum iron estimations were carried out by a modification of the method of Dahl (1948) in which the iron is oxidised by nitric acid and the colour is developed by potassium thiocyanate The danger of co-precipitation of some of the serum iron along with the proteins is obviated in this procedure by the denaturation of the proteins by heat before their precipitation with trichloracetic acid

Urinary and fæcal iron was measured as follows An aliquot of the specimen was dry ashed, the ash being dissolved in iron-free hydrochloric acid and four drops of nitric acid added to the hot solution After cooling, 2 c c of 20 per cent potassium thiocyanate was added, the solution centrifuged and the colour compared with the standard in a Spekker photoelectric absorptiometer *

Response to Intravenous Iron of Patients Refractory to Iron Preparations given by Mouth —In Table I there are given the results of intravenous iron therapy in 13 patients with hypochromic anæmia who showed no response to the prolonged administration of iron by mouth It will be seen that in all these patients there was a satisfactory rise in hæmoglobin

The following information about these patients is of interest

Cases 1, 2 and 3 were examples of the sprue syndrome, a condition in which the clinical features are the direct result of malabsorption and the anæmia is frequently refractory to the usual forms of treatment Six months after Case 1 had been treated with 1 8 gm of ferrivenin, the patient developed a macrocytic anæmia with a megaloblastic marrow, which failed to respond to liver injections (vitamin B_{12} not then being available) but responded readily to folic acid When the patient was seen six months later, there was no return of the iron deficiency anæmia despite the fact that no further iron therapy had been given

In Case 5, although fat-balance tests revealed no evidence to support a diagnosis of the sprue syndrome, the hæmatological features

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* This work was done in 1948 and 1949 More recently other workers have obtained significantly higher results in estimating serum iron levels, but this in no way detracts from the validity of the comparisons or conclusions—L S P Davidson

TABLE I

Response to Intravenous Iron of Patients Refractory to Iron Preparations given by Mouth in Hospital

Name	Age	Sex	Cause of Anæmia	Blood Findings before Injections			Gm of Iron given I V	Blood after Injections		
				Hb (per cent)	R B C (M/c mm)	C I		Hb (per cent)	R B C (M/c mm)	C I
1 M F	35	F	Steatorrhœa	56	3 49	0 80	1 8	100	4 80	1 04
2 B L	13	F	Cœliac disease	62	4 50	0 69	0 5	90	4 48	1 00
3 W S	22	M	Cœliac disease	56	4 69	0 60	1 2	102	5 01	1 02
4 M G	41	F	Idiopathic	56	4 01	0 70	1 2	90	4 80	0 94
5 M C	61	F	Idiopathic	62	4 32	0 72	1 0	100	5 00	1 00
6 I M	58	F	Gastro enterostomy	62	3 74	0 83	1 2	108	5 00	1 08
7 A G	39	F	Partial gastrectomy	48	4 32	0 56	1 0	100	4 84	1 03
8 A M	74	F	Idiopathic	64	3 74	0 86	0 7	94	4 46	1 05
9 H M	38	F	Idiopathic	64	4 00	0 80	1 1	96	5 24	0 92
10 R H	37	F	Idiopathic	68	5 41	0 63	1 0	102	4 50	1 13
11 J M	40	F	Idiopathic	50	3 56	0 70	1 1	100	4 90	1 02
12 W B	26	F	Idiopathic	66	4 82	0 68	1 2	90	5 00	0 90
13 A M	35	F	Pregnancy	54	4 12	0 66	1 5	86	4 46	0 96

were somewhat similar The patient had a refractory idiopathic iron-deficiency anæmia with a normoblastic marrow and received intensive oral iron therapy for a year with no response The marrow then became megaloblastic and a hypochromic macrocytic blood picture developed in the peripheral blood There was no response to the refined liver preparation " Anahæmin " but a rapid response ensued when folic acid was given, the marrow reverting to the normoblastic state with an associated rise in red cells Despite this, the refractory iron deficiency persisted until treatment with " Ferrivenin " was given

These two cases support the view of Davidson and Girdwood (1947) that certain cases of " idiopathic " refractory megaloblastic anæmia are probably due to malabsorption despite the absence of diarrhœa or steatorrhœa

TABLE II

Iron Absorption Tests in Normal Individuals
Serum Iron (μg per 100 ml Serum)
(Test dose = 18 grains of ferrous sulphate)

Name	Fasting Level	2 Hour Level	4 Hour Level	6 Hour Level	Rise in Serum Iron.
J D	53	200	160	103	147
I G	64	166	200	116	136
M B	40	56	175	133	135
N H	58	183	146	140	125
M W	40	230	250	80	210
C H	106	220	193	160	114
		Average maximal rise in serum iron = 145			

Case 6 had a gastroenterostomy and Case 7 a subtotal gastrectomy it is reasonable to assume that malabsorption played some part in the failure of these patients to respond to oral iron therapy In the remaining cases in Table I no satifactory explanation of their refractoriness to oral therapy was discovered Accordingly it was decided to make an investigation of the absorption of iron in normal individuals and in patients suffering from anæmia of various types

Iron Absorption Curves in Normal Individuals—Curves were carried out on six apyrexial patients in whom the blood picture and blood count were normal The test dose of 18 grains of ferrous sulphate was given by mouth The results are given in Table II

The average rise in serum iron in these cases was 145 μg per 100 ml the maximal being 210 μg per 100 ml , the minimal 114 μg per 100 ml Accordingly a rise in serum iron of 100 μg per 100 ml is here taken to be the arbitrary lower limit of normal in persons receiving a dose of approximately 4 mg of iron per kilogram of body weight Any curve showing a smaller rise than 100 μg per 100 ml is considered to be abnormally flat If this be true for normal persons it is even more significant for anæmic patients since Balfour, Hahn *et al* (1942) have shown that there is increased absorption of iron in anæmic individuals

Iron Absorption Curves in 19 Cases of Iron-Deficiency Anæmia—The results are as shown in Table III An average rise in serum iron of 236 μg per 100 ml was obtained, a figure which suggested that satisfactory absorption of iron had occurred This suggestion received confirmation when it was shown that subsequently all these patients responded satisfactorily to iron preparations given by mouth

Iron Absorption Curves in Allegedly Refractory Iron-Deficiency Anæmia—It has been the experience of the staff at the Hæmatological Clinic at Edinburgh Royal Infirmary that many patients with so-called " refractory " iron-deficiency cease to be refractory when iron therapy is given in hospital This is usually due to the patient on treatment at home taking the iron preparation irregularly

Twenty of the patients referred on account of such a " refractory " state had iron absorption tests carried out The results are given in Tables IVA and IVB

A study of Table IVA shows that cases 1-15 absorbed iron satisfactorily as judged by the rise in serum iron, and responded satisfactorily to subsequent oral iron therapy

It will be seen from Table IVB, on the other hand, that five flat curves were obtained in Cases 16-20

In none of these cases was there any response to continued oral iron therapy given under supervision, although the patients all responded dramatically to subsequent parenteral iron Unfortunately this form of therapy had to be abandoned in Case 16 because of severe reactions This is the only case in this series in which unpleasant reactions to " Ferrivenin " were encountered The information given in Tables II, III and IV is summarised in Graph 1

Iron Absorption Curves in Macrocytic Anæmia—Absorption tests carried out on 10 patients are shown in Table V Cases 1-7 had Addisonian pernicious anæmia and 8-10 had macrocytosis with normoblastic or macro-normoblastic marrow

The average fasting serum iron for the ten curves was 138 μg / 100 ml with a rise of only 27 μg /100 ml and that for the 7 cases of pernicious anæmia was 174 μg /100 ml with a rise of 18 μg /100 ml

In cases 9 and 10 there was iron deficiency in addition to macrocytosis Case 9 had a markedly shortened small intestine due to previous gut resection The anæmia responded to parenteral iron given with protein, vitamins and folic acid by mouth

The serum iron level in pernicious anæmia invariably falls within the first few days after specific treatment (Cartwright *et al*, 1948) This is supposedly due to the rapid utilisation of the iron by the newly formed red cells and usually follows the reticulocyte rise The fall is more precipitate in those cases receiving vitamin B_{12}, liver or folic acid by injection than by mouth

TABLE III

Iron Absorption Curves in Cases of Iron Deficiency Anæmia

(Test dose = 18 grains of ferrous sulphate)

Case	Blood before Treatment				Serum Iron Levels in μg per cent					Blood after Treatment with Oral Iron					Period of Treatment in Weeks
	Hb	R B C M /c mm	C I	P C V per cent	Fasting	2 hrs	4 hrs	6 hrs	Rise	Hb per cent	R B C M/c mm	C I	P C V per cent	Serum Iron μg per cent	
1	59	4 1	0 72	28 5	35	250	110	115	215	82	4 78	0 86	33 7	110	4
2	36	3 76	0 48	26 7	18	200	304	66	286	78	4 55	0 86	34 0	76	4
3	53	4 74	0 56		58	145	217	156	159	84	5 01	0 84		72	4
4	27	3 19	0 42	17 2	16	153	266	66	250	63	3 96	0 80	31 0	64	5
5	67	4 53	0 74	35 4	50	310	240	110	260	88	4 86	0 90	41 0	110	4
6	43	3 43	0 63	24 2	46	196	250	130	204	84	4 68	0 90	40 0	114	2
7	36	3 84	0 47		47	305	160	72	258	94	4 8	0 98		108	9
8	45	4 35	0 52	27 0	32	393	95	33	361	67	5 01	0 67	30 0	56	2
9	42	4 60	0 46	27 2	36	126	295	216	259	88	4 90	0 90	38 0	80	5
10	46	4 24	0 54	27 8	60	220	106	100	160	75	4 90	0 80	35 1	86	4½
11	60	4 30	0 70	30 7	65	358	140	130	293	90	4 52	1 0	40 6	125	3½
12	66	4 72	0 71	34 0	36	156	190	183	154	97	4 98	0 97	45 7	108	4
13	50	3 9	0 64	29 0	18	290	180	129	272	90	4 86	0 93	39 6	96	5
14	42	3 96	0 53	24 0	40	290	266	170	250	90	5 01	0 90	38 0	75	8
15	47	3 63	0 65	23 1	58	85	217	117	159	75	4 26	0 88	37 2		8
					Average maximal rise in serum iron = 236										
16	50	4 20	0 60		26	250	202	80	224	84	4 60	0 91		92	6
17	72	4 20	0 86	26 9	68	360	180	133	292	97	4 98	0 97	45 7	80	3
18	80	4 98	0 80	38 2	76	105	233	160	157	104	5 01	1 04	40 0	108	4
19	46	4 32	0 53	27 5	46	356	144	80	310	100	5 00	1 0	42 0	96	12
					Average maximal rise in serum iron = 238										

TABLE IVA

Iron Absorption Curves in Patients Allegedly Refractory to Iron by Mouth

(Test dose = 18 grains ferrous sulphate)

Case	Blood before Treatment in Hospital				Serum Iron Levels in µg per cent					Weeks of Treatment	Blood after Oral Iron Therapy in Hospital				
	Hb per cent	R B C M/c mm	C I	P C V per cent	Fasting	2 hrs	4 hrs	6 hrs	Rise		Hb per cent	R B C M/c mm	C I	P C V per cent	Serum Iron µg per cent
1	28	2 66	0 55		33	120	283	97	250	4	58	3 38	0 86		80
2	66	4 66	0 71	32 8	53	174	277	217	224	8	94	5 00	0 94	39 0	92
3	67	4 20	0 80	33 9	16	140	185	46	169	1½	78	4 30	0 91	36 0	40
4	51	4 41	0 58	29 2	26	113	300	100	274	5	80	4 50	0 89	39 0	78
5	36	3 74	0 48	27 0	44	103	210	183	166	7	84	4 68	0 90	39 0	106
6	69	4 72	0 73	35 0	40	240	85	95	200	2	86	4 98	0 86	40 0	92
7	32	3 77	0 42	20 0	33	50	175	60	142	8½	90	4 86	0 93	39 5	88
8	59	4 25	0 69	30 7	30	177	292	58	262	9	106	5 00	1 06	41 0	94
9	63	4 44	0 71		66	300	290	375	309	5	86	4 68	0 92	38 0	106
10	47	3 75	0 63	25 0	20	198	246	186	226	3	58	4 00	0 73	28 0	76
11	52	4 01	0 65		30	200	158	183	170	8	76	4 50	0 84	29 0	82
12	76	4 80	0 79		45	245	192	110	200	8	100	5 08	0 98	39 0	80
13	58	4 98	0 58	28 0	25	298	210	178	273	9	88	4 9	0 90	36 0	94
14	62	4 20	0 74	31 0	43	241	173	90	198	6	92	4 8	0 96	42 0	118
15	57	4 84	0 59	33 4	48	129	330	295	282	5½	91	5 50	0 83	41 0	130

Average maximal rise in serum iron = 223

Cases showing satisfactory iron absorption and subsequent response to oral iron therapy

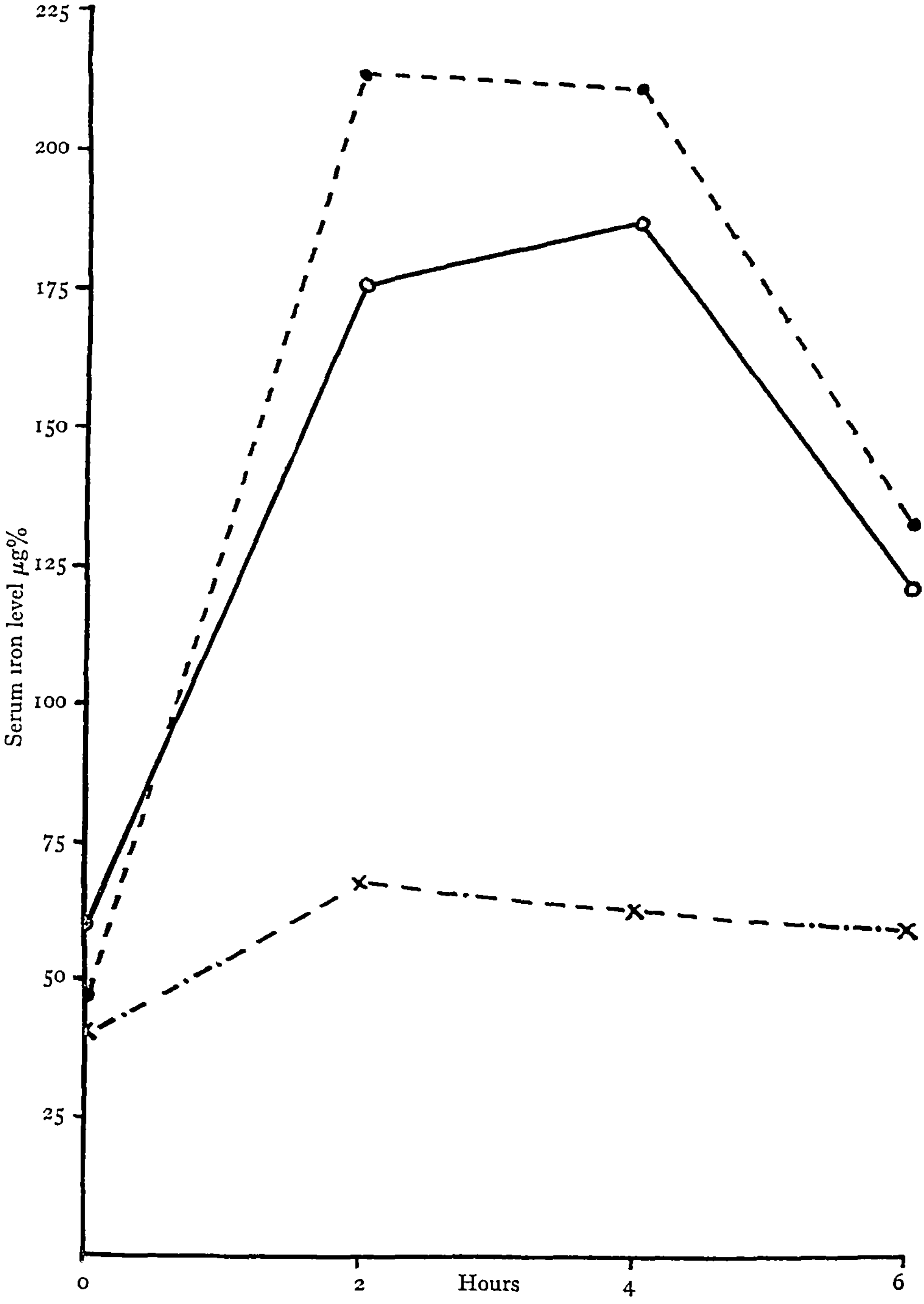
TABLE IVB

Iron Absorption Curves in Patients Allegedly Refractory to Iron by Mouth

(Test dose = 18 grains ferrous sulphate)

Case	Blood before Treatment				Serum Iron Levels in µg per cent					Blood after Treatment with Iron by Mouth in Hospital				Blood after Intravenous Iron					Gm I V Iron given
	Hb per cent	R B C M/c mm	C I	P C V per cent	Fasting	2 hrs	4 hrs	6 hrs	Rise	Hb per cent	R B C M/c mm	C I	P C V	Hb per cent	R B C M/c mm	C I	P C V	Serum Iron µg per cent	
16	48	3 52	0 68	27 5	46	67	63	67	21	50	3 42	0 73	28 5	66	4 28	0 77	29 0	58	0 28
17					46	63	63	43	17	50	3 56	0 70	28 0	101	5 37	0 94	43 0	65	1 10
18	55	4 80	0 57	30 0	20	56	66	74	54	54	4 99	0 54	30 0	98	5 01	0 98	42 0	84	1 00
19	38	3 23	0 59	22 5	30	66	58	47	36	39	3 30	0 59	23 0	80	5 10	0 78	38 8	90	1 10
20	51	4 32	0 59	28 3	58	83	66	66	25	52	4 20	0 62	30 0	82	4 41	0 93	39 5	96	1 0
					Average maximal rise in serum iron = 31														

Cases showing poor iron absorption and subsequently no response to oral iron therapy but a good response to intravenous iron



○————○ Normal individuals (mean of 6 cases)

● — — — ● Anæmic patients who responded to oral iron (mean of 34 cases)

× — — —× Anæmic patients who failed to respond to oral iron but responded to intravenous iron (mean of 5 cases)

GRAPH 1 —Iron absorption curves
Test dose = 18 grains ferrous sulphate given at time " 0 " by mouth

TABLE V

Iron Absorption Curves in Macrocytic Anæmias

Case	Peripheral Blood						Marrow Reaction	Serum Iron Levels µg /100 ml				
	Hb per cent	R B C M/c mm	C I	P C V per cent	M C V cµ	M C H C per cent		Fasting	2 hrs	4 hrs	6 hrs	Rise
1	38	1 48	1 28	15 0	101 3	37 4	Megaloblastic	144	153	145	156	12
2	66	2 60	1 26				,,	213	208	217	233	20
3	50	1 96	1 27	22 0	112 2	33 6	,,	113	113	140	108	27
4	66	2 59	1 27	29 0	111 9	33 6	,,	200	193	233	160	33
5	75	2 60	1 40	32 0	123 0	34 6	,,	213	203	217		4
6	50	2 07	1 20	21 0	101 4	35 2	,,	180	180	213	200	33
7	35	1 25	1 40	15 0	120 0	34 5	,,	156	137	144	110	0
8	84	3 58	1 17	33 9	94 6	36 6	Normoblastic	47	53	80	53	33
9	62	2 60	1 19	33 3	128 0	27 5	Macro normoblastic	49	76	33	46	27
10	46	2 12	1 08	22 0	103 7	20 9	Normoblastic	63	141	100	63	78
								Average rise in serum iron = 27				

EXCRETION OF IRON

The iron content of the body is mainly regulated by controlled absorption Since the use of intravenous iron therapy has become more popular, it has become a matter of great importance to know to what extent the body is able to excrete iron, since, if the body cannot dispose of excessive amounts of iron introduced into the blood stream, there is a grave danger that a condition similar to hæmochromatosis may occur

Accordingly several experiments were carried out in an attempt to measure the excretory capacity of the body

1 Measurement of the normal range of urinary iron
2 The effect of intravenous injections of 100-300 mg Ferrivenin on the urinary and fæcal iron
3 The effects of oral iron therapy, transfusion and hæmolysis on the urinary iron

1 *Normal Range of Urinary Iron*—There is a wide variation in the published figures for urinary iron Widdowson and McCance (1937) give a maximum twenty-four hour level of 0 15 mg while Barer and Fowler (1938) give a range varying from 0 8 to 1 03 mg Because of this discrepancy of findings we carried out estimations on 50 patients who were having neither oral nor intravenous iron therapy We found that the range lay between 0 10 and 0 40 mg with an average of 0 23 mg per twenty-four hour specimen

2 *Effect of Intravenous Ferrivenin on Urinary and Fæcal Iron*—Nine balance experiments were carried out This involved estimation of urinary and fæcal iron for three to four days both before and after the intravenous injection of iron The patients were put on to a diet of known iron content After 5 cases had been completed it was evident that the fæcal iron varied only in so far as the diet and bowel action varied and was not affected by the iron injections This part of the investigation was therefore omitted in cases 6-9 The initial injection consisted always of 200 mg iron, but subsequent doses varied in size on two occasions The results are shown in Table VI

These experiments demonstrate the following features of iron excretion —

(*a*) There is no apparent iron excretion into the intestinal tract
(*b*) The kidneys are capable of limited iron excretion varying from 2 9 to 4 4 per cent of a 200 mgm injection
(*c*) Urinary excretion of iron is not directly related to the hæmoglobin level

3 *Effect of other Conditions upon Urinary Iron*—Iron balances were carried out in patients who were receiving oral iron therapy or blood transfusions and in cases of hæmolytic anæmia and polycythemia In no case was there any significant elevation in the urinary iron level

TABLE VI

Iron Balance Experiments

Urinary Iron (mg)								Fæcal Iron (mg)			
Case	Presence of Iron Deficiency	Before Injection 3 Day Average	After Injection			Mgm Ferrivenin Injected	Per cent Dose Excreted in Urine	Daily Average			Per cent Dose Excreted in Fæces
			1st Day	2nd Day	Average 3rd and 4th Day			3 Days Before	1st Day After	1st 3 Days After	
1	Yes	0 265	8 18	1 10	0 263	200	4 4	6 8	0	6 6	0
2	Yes	0 22	7 20	0 38	0 21	200	3 6	10 3	15 2	8 1	0
3	Yes	0 17	8 57	0 22	0 21	200	4 2	9 7	0	8 5	0
4	(*a*) No	0 29	8 33	0 54	0 29	200	4 2	12 4	10 5	10 2	0
	(*b*) No	0 29	11 90	1 58		300	4 3	7 5	4 25		0
5	(*a*) No	0 32	6 21	0 75	0 20	200	3 2	10 4	0	6 8	0
	(*b*) No	0 20	1 03	0 08		100	0 8	6 8	0	8 5	1 7
6	No	0 24	8 51	0 49	0 28	200	4 3				
7	Yes	0 29	8 46	0 14	0 23	200	4 1				
8	Yes	0 20	6 07	0 18	0 19	200	2 9				
9	Yes	0 18	7 80	0 68		200	3 8				

DISCUSSION ON THE VALUE OF IRON ABSORPTION CURVES

As has been noted by Moore *et al* (1939), the factors influencing the serum iron level are not only the extent of absorption of iron from the gut, but also of red cell destruction, iron utilisation, and excretion Nevertheless, the constancy of the present results is such that it is thought that significance may be attached to iron absorption curves provided sufficiently large quantities of iron are used as the test dose Kooyman (1949) carried out an extensive study of iron absorption curves using 225 mg of ferrous chloride, which contains 63 mg iron or approximately 1 mg iron per kilo body weight In our experience this dose is too small to have value and hence we consider that the dose should be approximately 4 mgm iron per kilo body weight

A rise in serum iron of anything above 100 μg /100 ml when the technique described above is used appears to indicate the presence of satisfactory iron absorption From experience in the present series of experiments it is considered that most cases of hypochromic anæmia showing a rise above 100 μg /100 ml can be expected to respond to oral iron given under supervision

In addition to patients suffering from malabsorption there is a group with no evidence of blood loss, splenic anæmia, carcinoma, faulty diet or diarrhœa, whose serum iron curves are persistently flat (See idiopathic cases, Table I and also Table IVB) The anæmia is refractory to iron given by mouth, but responds to parenteral iron therapy It is considered that the defect in these cases is in the absorption of iron

CLINICAL INDICATIONS FOR INTRAVENOUS IRON

There is a limited but very definite place for parenteral iron treatment in clinical medicine But it should be stressed that the vast majority of patients with iron-deficiency anæmia will respond to oral iron therapy, and a reasonable trial with oral preparations should be made before resorting to intravenous iron

The indications for its use are as follows —

1 Persistent gastro-intestinal disturbance from taking oral iron This is most commonly found in pregnancy and it is in these cases that we have found Ferrivenin most useful
2 Malabsorption of iron due to persistent diarrhœa, steatorrhœa, gastric or small gut resection and in the rare case of idiopathic malabsorption of iron
3 Rheumatoid arthritis In this condition there is sometimes a beneficial effect on the general condition of the patient as well as on the anæmia which may be refractory to oral iron therapy
4 For the rapid restoration of the body's depleted stores of iron following massive external loss of blood

SUMMARY

1 *Iron absorption tests* were carried out in

(*a*) Six normal persons
(*b*) Thirty-four patients with hypochromic anæmia who subsequently responded to oral iron therapy
(*c*) Five patients with hypochromic anæmia who were refractory to oral iron therapy but subsequently responded to intravenous iron

Refractoriness to oral iron therapy was related to a failure in absorption as indicated by a flat iron absorption curve

2 Investigations into the excretion of iron following intravenous iron therapy showed that none of the iron administered by this route was excreted in the fæces but that up to approximately 4 per cent of the dosage given might be excreted in the urine

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REFERENCES

Balfour, W M , Hahn, P F , Bale, W F , Pommerenke, W T , and Whipple, G H (1942), *Journ Exp Med* , 76, 15
Barer, A P , and Fowler, W M (1938), *Journ Lab Clin Med* , 23, 148
Cartwright, G E , Huguley, C M , Ashenbrucker, H , Fay, J , and Wintrobe, M M (1948), *Blood*, 3, 501
Dahl, S (1948), *Brit Med Journ* , 1, 731
Davidson, L S P , and Girdwood, R H (1947), *Brit Med Journ* , 1, 587
Davidson, L S P , and Girdwood, R H (1948), *Brit Med Journ* , 1, 733
Govan, A D T , and Scott, J M (1949), *Lancet*, 1, 14
Kooyman, J C (1949), *Acta Med Scand* , 134, 205
Moore, C V , Arrowsmith, W R , Welsh, J , and Minnich, V (1939), *Journ Clin Invest* , 18, 553
Moore, C V , and Doan, C A (1936), *Journ Clin Invest* , 15, 455
Nissim, J A (1947), *Lancet*, 2, 49
Sinclair, R J G , and Duthie, J J R (1949), *Lancet*, 2, 646
Sinclair, R J G , and Duthie, J J R (1950), *Brit Med Journ* , 2, 1257
Slack, H G B , and Wilkinson, J F (1949), *Lancet*, 1, 163
Widdowson, E M , and McCance, R A (1937), *Biochem J* , 3, 2029

NEUROLOGICAL COMPLICATIONS OF SOME INFECTIOUS DISEASES

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THE most interesting condition among those due to infectious diseases is the disseminated encephalomyelitis which sometimes follows, increasingly so in recent years, measles, vaccinia, whooping cough, chicken-pox and mumps

Underwood (1935) mentions the increasing incidence of central nervous system complications of infectious diseases and post-vaccinia in the previous thirty years

Henderson (1952) notes that involvement of the central nervous system has become increasingly frequent in mumps during the last forty years, and *Malamud* (1937) noted an increasing number of reports of measles encephalomyelitis There does not appear to be general agreement about the cause of these conditions and their classification is therefore difficult Several theories of causation are discussed at present and have been mentioned by Underwood (1935) and by Ford (1944)

(i) Since the histological nature of the lesions seems to be essentially the same whether the condition has followed measles, vaccinia or some other illness, it has been suggested that the process is due to some neurotropic virus which becomes activated by the primary infection, or, alternatively, which invades the central nervous system when the patient's resistance is lowered by illness The same clinical picture may develop after obscure febrile illnesses or apparently without recognisable illness This hypothetical virus has not been demonstrated

(ii) Some authorities believe that the virus of the original disease actually invades the central nervous system (Malamud, 1937)

(iii) Another possibility is that of demyelinating toxins produced by the virus of the original infection, and Ford (1944) considers it possible that a number of filtrable viruses may produce a series of toxins which have a similar effect on myelin

(iv) A suggestion, based on a study of paralysis following anti-rabies inoculation, has been put forward that the destruction of myelin, and the consequent nervous symptoms, is due to allergic reactions or the formation of antibodies

(v) The condition may be fortuitous

On the whole, it may seem from the recent behaviour of those infectious diseases which affect the central nervous system that the encephalomyelitis following an infectious disease such as, for example, varicella is due to the development of neurotropism by the virus of varicella itself

It has been noted by Underwood (1935), and recent evidence tends to corroborate that an epidemic peak occurs after epidemics of influenza and poliomyelitis

In this county the incidence of notified poliomyelitis is shown in the appended table

	1942	1943	1944	1945	1946	1947	1948	1949	1950	1951
Poliomyelitis	6	0	0	0	2	10	0	2	29	1

In 1950 the epidemic of poliomyelitis commenced in July and reached its peak in September and waned in December The greatest number of neurological complications of infectious disease occurred in December 1950 and January, February and March 1951 (8 cases) There was also a widespread epidemic of influenza in January 1951

The encephalopathy associated with pertussis is striking and apparently characteristic and may be specific It has been variously attributed to vasomotor disturbances, to air-embolism and to bacterial toxin At present, the last-named possibility would appear to be the most attractive It is believed that the process may cause permanent brain damage with persisting symptoms in children who survive the encephalopathy It is possible that the lesions are analogous to the cloudy swelling of the kidneys and other viscera found in almost all acute and fatal illnesses and that they are the anatomical basis of delirium and stupor (Ford, 1944)

MEASLES

It is probable that encephalomyelitis occurs more commonly with measles than with any other infectious disease of childhood, although the incidence is low even with measles Figures showing the incidence of encephalomyelitis in measles epidemics must be very rough approximations as the complication is rare in some epidemics and common in others

In four relatively large epidemics in a rural area neurological complications were observed during two epidemics and no complications noted in two other epidemics Cases occurred in small groups in such a way as to suggest an epidemic, *e g* in the 1947 epidemic of measles, 2 cases of severe encephalomyelitis were seen—one of whom died, and the other, although crippled, still survives

In the 1950-51 epidemic, 6 cases were seen Four were mild and recovery was complete One, which was severe, has a residual paraparesis and the other has mental and personality changes There is no obvious tendency to select either sex and the age incidence coincides with that of measles (viz 1-10 years) As a rule, it is said to occur in severe cases of measles but in the cases under review, measles was relatively mild A number of syndromes occur, although there is, of necessity, much overlapping

1 Symptoms of diffuse cerebral involvement of brief duration—often termed " meningism "
2 Multiple focal or diffuse lesions in the nervous system
3 Single focal cerebral lesions
4 Cerebellar syndromes
5 Spinal syndromes
6 Optic neuritis
7 Mental and personality changes

1 *Symptoms of Diffuse Cerebral Involvement of Brief Duration* (*Meningism*) —The onset is usually between the fourth and fifth day of the eruption, *i e* at the beginning of convalescence, with drowsiness and even stupor This may deepen into coma Headache, vomiting, muscle twitching or convulsions follow in a few hours Evidence of meningeal irritation is present The course is short, and despite the alarming initial symptoms, the child is well in two or three days, but may show some irritability and lack of emotional control for several weeks Cerebro-spinal fluid is under pressure and may show a moderate increase in cell count, globulin and total protein Symptoms and signs point to an intoxication of the brain rather than meningeal involvement and the neck stiffness may be merely part of the generalised muscular rigidity

The features of this group are the absence of focal signs and the quick and complete recovery Four cases of this kind were seen during the epidemic which occurred in the first quarter of 1951 All occurred when the rash was fading and were of varying degrees of severity

Case Reports —Four cases Two of these were in girls of 5 and 7 and were mild, showing an initial convulsion with unconsciousness for four to six hours Bilateral extensor toes were present during this period, which was followed by a transient confusional phase Complete recovery occurred during the following few hours

One moderately severe case in a boy of 8 years had three separate convulsions with unconsciousness for six hours and followed by disorientation, confusion and inco-ordination for about twelve hours Complete recovery followed

One severe case was in a boy of 10 years who gave a history of mumps three months previously and repeated upper respiratory infections during the school year On the fourth day of the rash he had a severe convulsion and was admitted into hospital five hours later He had two further fits after admission Plantar responses were extensor and tendon and superficial reflexes were not elicited Neck stiffness, Kernig's sign, optic neuritis and a generalised muscle rigidity were present He had one other fit on the next day and was unconscious for two days The cerebro-spinal fluid was normal He recovered slowly and was normal when discharged five days later and had no residual symptoms or signs when followed-up five months later These cases were seen during January and February 1951 There was no history of migraine, epilepsy or other neuropathy in the family histories of these cases

2 *Multiple Focal or Diffuse Lesions in the Nervous System*—The onset is identical with the "meningism" type with similar physical signs There is rigidity of muscle although atonia may occur Myoclonic twitching may be present Cranial nerve palsies are rare but the VI nerve may be involved Paralysis of the bulbar muscles may occur and the child may die Usually recovery begins after several days with a return of consciousness Paraplegia and paraparesis may be found as sequelæ, but hemiplegias and monoplegias are uncommon Pareses are as a rule spastic, but atrophic and flaccid muscles may be found Choreic and athetoid movements have been described and speech disturbances may occur, due to bulbar palsy or cerebellar involvement or partial aphasia Mental changes, with irritability, screaming and obscene language may be present Sleep is usually irregular but prolonged somnolence may occur Improvement is slow and symptoms may not disappear for years Defects in intelligence may follow

Ford (1928) notes complete recovery in 14 of 42 cases and 5 deaths The remaining cases showed mental defect or personality change, disturbances of motility, epilepsy and narcolepsy

Case Report—exemplfying multiple lesions with a residual paraparesis in a girl of 3 years 7 months She was admitted 2 2 51 with a history of a measles rash five days previously and on the day of admission she had neck rigidity, champing of the jaws, and athetoid movements of the hands and arms Feeds were refused She was lying supine with her eyes to the left Extensor plantar responses and optic neuritis were present The following day tendon reflexes were exaggerated with tremor and twitching of the arms Two days later, tendon reflexes were absent and bilateral VI nerve weakness was present Four days later the lower limbs were spastic She commenced talking twenty-four days after admission and was until that time spoon-fed by the nursing staff There was gradual improvement until her discharge from hospital six weeks after admission

At a follow-up examination four months later, she was found to be a happy and exceedingly talkative child with a residual paraparesis not interfering considerably with walking During this illness, meningism, involvement of the II and VI cranial nerves occurred with, possibly, some change in personality The cerebro-spinal fluid was under slightly increased pressure, with a slight increase in lymphocytes and protein

3 *Signs of Single Focal Cerebral Symptoms*—Hemiplegia, aphasia or hemianopia may occur in association with those symptoms already mentioned, but usually in an apoplectic fashion like a gross vascular lesion, with convulsions and coma for a time It is probable that these cases bear a less direct relation to measles than exists in other groups of cases They probably result from a non-specific effect on the vessel walls which may occur in any febrile illness

Case Report—A girl—the seventh of eight children, her parents and siblings were healthy and apparently normal, although her father was not of average intelligence She was born normally on 5 5 43 and developed normally She suffered from convulsions with the onset of teething and thereafter at approximately three-monthly intervals The attacks were preceded by irritability, vomiting, drowsiness and pyrexia and lasted for about three-quarters of an hour

She was said to be a nervous and sensitive child She had been threatened by her father that measles would follow any " wrong " action She was admitted on 13 7 48 aged 5 years 2 months with a history of a mild attack of measles two weeks previously She was convalescent on the fifth day and went to see a friend She was said to have been " teased " about measles and ran home to bed She was completely withdrawn for three days with refusal of food and no speech Fluids had been taken for three days prior to admission On examination, she was a withdrawn, dehydrated child with stiffness of the neck and of the left arm and left leg No other abnormal feature was found and the C S F was normal She continued to refuse food and developed twitching of the limbs Parenteral fluids with calcium and vitamin D were given She became more and more withdrawn, with occasional outbursts of obscenity and a left hemiplegia with a spasticity varying in degree from day to day There was obvious mental deterioration which daily increased and on 3 9 46, six weeks after admission and two months after the onset of measles, she died—demented and hemiplegic Consent for autopsy was not obtained

4 *Cerebellar syndromes* —While purely cerebellar syndromes are apparently unusual, signs of cerebellar ataxia including loss of muscle tone, scanning speech, nystagmus, intention tremor, and typical gait may occur These disabilities are revealed by the child's increasing activity during convalescence Cerebellar ataxia is said to be the most striking feature of measles encephalomyelitis, and measles may be responsible for a large proportion of the so-called acute cerebellar ataxias Skoog (1920) mentions that signs may develop gradually without other nervous manifestations

CASE REPORT —A boy of 6 years 9 months was admitted on 21 9 47 with a history of an attack of measles in July 1947 His disability was observed in the early days of convalescence He fell easily during attempts at walking and about a month later was noticed to be dragging his right leg and unable to use his right hand The right plantar response was extensor and Rombergism was present There was gradual return to normality but an ataxic gait persisted His left arm, hand and leg were cyanosed and cold Gradually a drooping stance and an unsteady shuffling gait became evident There was symmetrical wasting of hands and arms, and feet and legs with poor muscle tone In spite of attempts at re-education there has been no substantial improvement in his condition since 1948 when he was previously examined

5 *Spinal Syndromes* —Present as an acute ascending paralysis, or a transverse myelitis, flaccid at first and then spastic although there may be atrophy of muscle groups

Ford (1928) mentions deaths from respiratory paralysis in some patients, recovery in approximately one half of the cases and residual motor weakness of various types, including muscular atrophy, in about one-third of the cases

6 *Optic neuritis* —Most cases show a mild optic neuritis or œdema of the optic disc

7 *Mental and Personality Changes* —Mental disturbances are not uncommon, an initial delirium having been noted in a high proportion of the cases

During convalescence, transient mental disturbances are common and prolonged toxic psychoses may occur Fear, excitement and manic or depressive manifestations have been observed and also delirium and hallucinations, both auditory and visual The role of the patient's personality and hereditary background is obviously a large one as there is nothing specific in the measles toxin The commonest residuum is a reduction in intelligence Malamud (1939) describes one hyperkinetic case with excitement and uncontrolled activity

CASE REPORT —A boy of 11 years and 4 months was first seen on 13 3 52 He was the fifth of seven children and had been born normally at full term There was no history of intra- or neo natal anoxia and he had developed normally He had whooping cough and chicken-pox at nine months but there was no history of convulsions He had a mild attack of measles in March 1951 Prior to this illness he had been a quiet obedient child but gradually, following the illness, he became increasingly talkative and showed increasing and uncontrolled activity He became unable to concentrate at school having previously been a good scholar He had truanted on a number of occasions There had emerged gradually a completely irresponsible type of behaviour and a lack of appreciation of his misdeeds Over a course of months, corporal punishment and exhortations had failed to produce any result

On examination, he was a calm, talkative boy with no evidence of organic lesion in the central nervous system He could not deal with psychometric tests It was discovered later that one of his siblings had been under treatment for schizophrenia The diagnosis of nervous complications is reasonably easy with a history of measles or a fading eruption, but a case of long duration will present obvious difficulties Poliomyelitis and tuberculosis must be considered in the initial diagnosis The outlook is favourable and the percentage mortality is probably very low as a number of mild cases are not taken into consideration More than half the survivors are said to show evidence of central nervous system damage

Spastic paraplegia is the commonest residual disability and cerebellar ataxia is frequent, but some observers state that mental changes of varying degrees of severity are commonest Mental changes are, however, usually very mild Epilepsy is a not unusual sequel and among rare disturbances are narcolepsy and precocious menstruation with obesity (Ford and Guild, 1937)

POST-VACCINIAL ENCEPHALOMYELITIS

Attention was first drawn to this condition in 1932 although complications of vaccinia had been previously noted by Turnbull and Macintosh (1926) and Ford and Wilson (1927) Symptoms first appear nine to eleven days after vaccination although intervals of from two to twenty-five days have been described It may even follow unsuccessful vaccination The onset is said to be abrupt with headache, fever and vomiting, and convulsions with meningism Stupor and coma are said to be present and the clinical picture as a whole is similar to measles encephalomyelitis The mortality is said to be high, but recovery in survivors is complete

CASE REPORTS —(i) A girl aged 9 months (D O B 14 6 46) was admitted into hospital on 13 3 47 She was born normally at full term and her birth weight was 7 lbs 2 oz She was breast-fed for three months and received adequate vitamin supplements Eight days after vaccination in December 1946 she commenced to vomit, and showed anorexia, loss of weight, constipation, a miliarial rash, marked irritability and cough There was some photophobia On examination, there was no evidence of central nervous system damage She had marked hypotonia and generalised muscle wasting and a mild respiratory infection The heart rate was 160 per minute There was no clinical and no radiological evidence of scurvy, rickets or primary tuberculosis The C S F was normal and there was no evidence of urinary infection She became increasingly stuporose and died of pneumonia seven days after admission Consent for autopsy was not obtained

(ii) A boy, aged 7 months was seen on 3 12 46 with a history of vaccination four weeks previously at the age of six months On the 9th day after vaccination he developed irritability, photophobia, anorexia and a miliarial rash Screaming attacks were described, with attempts at biting his parents and self mutilation There was insomnia He had a heart rate of 150 per minute and was markedly hypotonic with muscle wasting and absent tendon reflexes Two months after the first appearance of symptoms he was almost normal, and subsequent progress was satisfactory

(iii) A girl of 8 months, developed similar manifestations with extreme muscle wasting and hypotonia nine days after vaccination Owing to the marked irritability and domestic unrest caused, the child was admitted into hospital Investigations of the C N S were negative and no pathology was found elsewhere

These three cases, eight to nine days after vaccination, showed marked irritability, anorexia, sweating, loss of weight, rash, constipation, hypotonia and muscle wasting, tachycardia and insomnia The picture presented was similar in almost all respects to pink disease and complete recovery in the survivors did not occur for two to three months

Turnbull and Macintosh (1926) state that it is unusual to have any residual disability although one case with persistence of spasticity for several months is described

VARICELLA

This is a common infectious disease, but nervous complications are very rare Bullowa and Wishik (1935) found 5 cases of encephalomyelitis in 2534 cases of varicella Two were fatal The onset is from three to twenty-one days after the first appearance of the eruption, and only in rare instances do symptoms precede the eruption Drowsiness, irritability and anorexia precede severe symptoms of vomiting, convulsions and stupor which may develop abruptly Meningeal irritation is minimal or absent Consciousness is regained in a few hours to days and central nervous signs become evident Sensory loss is unusual Spinal, cerebellar, cerebral and cranial nerve syndromes have been described The clinical picture is almost identical with that of measles encephalomyelitis The first British case was reported in 1914 by Miller and Davidson, who described the onset of tremor, choreiform movements, and unsteady gait in a child on the fifth day of chicken-pox There was some disturbance of speech and difficulty in standing

Winnicott and Gibbs (1926) noted the onset of symptoms on the eleventh day of the disease in a girl of 2 years 10 months The symptoms included drowsiness, spastic weakness of the legs, urinary incontinence, increased tendon reflexes, bilateral Babinski response, dysphagia, dysarthria and squint C S F was normal and recovery took place in a few weeks

In another very small group of cases, symptoms were almost exclusively referable to the spinal cord Smith (1926) reports a case of spastic paraplegia in a boy of 7 years with the onset in the second week of the disease and incomplete recovery in one year

Wilson and Ford (1927) describe a case in which a boy of 3 developed spasticity on the seventh day with recovery in six weeks

Underwood (1935) quotes 119 cases previously described and adds one case of his own He notes the increasing frequency of nervous complications of infectious disease in the preceding thirty years, and mentions that cerebellar types are much commoner with varicella In 107 cases there were 12 deaths and 16 others showed sequelæ of various kinds The sex incidence in 110 cases was males 67, and females 43 He mentions that symptoms may develop before or after the eruption but more than three days before, or twenty days after, the appearance of the rash is quite exceptional In most cases the onset is four to ten days after the first appearance of the rash

Case Report —A boy who was born on 9 10 47 was admitted into hospital on 6 6 51 He was the seventh of eight children and was born normally at full term, his birth weight being 10 lbs 4 oz He was breast fed for two months, and according to his mother had developed normally There was no history of convulsions During the first week of the rash he was drowsy and vomited each day The last scab separated one week before admission, on which day the youngest sibling was suffering from chicken pox He was found to be unable to walk one week before admission, fell on to his knees and attempted to move about by crawling Tremor of his hands was noticed when he attempted to feed himself and he had to be fed by his mother On examination, he was drowsy and listless and had a fading eruption He was unable to walk There was a mild degree of engorgement of the right ear drum and numerous small discrete glands in the neck, axillæ and groins

He had a mild enlargement of the liver The cranial nerves were normal and the reflexes normal except for rather equivocal plantar responses There was no neck stiffness Spontaneous nystagmus, intention tremor, photophobia and marked hypotonia were present C S F and blood count were normal and W R was negative

Slow improvement took place until on 15 6 51, ten days after admission, and seventeen days after the onset of symptoms, he was walking with a festinant gait and a bowed head He was able to feed himself but had a mild intention tremor His face was devoid of expression On 20 6 51, three weeks after the onset of symptoms, he was standing up well but had a moderate degree of hypotonia and muscle weakness On 18 10 51 he was walking apparently normally but was an expressionless and dull-looking boy

WHOOPING-COUGH

Neurological complications are, directly or indirectly, the result of pertussis There is no evidence to incriminate a neurotropic virus Pertussis is well known to be a more serious condition in infancy than after the age of two years Almost all cases with neurological complications are said to occur before the age of two years These are not uniform as in measles but include a number of entirely different manifestations

The commonest type is characterised by the abrupt development of convulsions, most frequently at the height of the disease Convulsions are severe, frequent and usually generalised, but may be focal There is a high mortality and death is said normally to occur after the first convulsion Many cases exhibit tetany, and indeed convulsions have been attributed to tetany If death does not occur, various cerebral symptoms such as hemiplegia, monoplegia or diplegia may occur, and stupor or drowsiness may persist for a number of days Seizures may be recurrent The C S F is normal or blood-stained The lesions themselves may be due to multiple hæmorrhages or degenerative processes Recovery may be complete

In certain cases, the onset is insidious with drowsiness and stupor and infrequent convulsions, but with a fine twitching of the extremities (a so-called epilepsia partialis continua of cortical inflammation) This stage progresses into one of muscle rigidity with flexion of the arms and rigid adducted legs Speech is commonly lost Death may be due to a secondary infection Convulsions or drowsiness in pertussis are evidence of encephalopathy and may lead to a dementia with generalised muscular rigidity

Byers and Moll (1948) drew attention to a risk of the prophylactic use of pertussis vaccine which, up to that time, had not been recognised They mention 15 instances, over a period of ten years, in which acute cerebral symptoms developed within a period of hours after administration of the vaccine The ages varied from 5 to 15 months, and according to histories supplied by the parents, development was proceeding normally and there was no past history of convulsions The vaccines used were made by several manufacturers All but one case at the time of follow-up study or death showed evidence of impairment of the central nervous system which might still have been in the healing stage in 3 or 4

During the same period about twice as many children were seen in hospital suffering from the encephalopathy complicating pertussis itself They noted the preponderance of males and the high incidence of abnormalities of the central nervous system in the family histories In view of the impressive evidence of the effectiveness of prophylactic pertussis immunisation now accumulating it seems likely that babies are safer immunised than not

CASE REPORTS —(i) A girl of 2 years 1 month was admitted to hospital on 3 2 51 with whooping-cough for two weeks, having been treated at home with chloramphenicol and eumydrin Vomiting had been particularly severe On admission there was diarrhœa, tachypnœa and tachycardia She had evidence of hypertelorism, a mild stupor and generalised flaccidity with continuous twitching of the hands Calcium gluconate and calciferol were given by intramuscular injection With increasing stupor, flaccidity and dysphagia the tendon reflexes disappeared C S F was normal with a pressure of 130 mm Loss of speech occurred and there was continuous fine twitching of the mouth, tongue and hands She could not take food, but as rooting and sucking reflexes were observed by accident, bottle feeding was successfully accomplished Two weeks after admission she became more co-operative, interested in toys, parents and nurses, sitting up unaided and aware of her environment She spoke a few words, resented bottle feeding and took a light normal diet Two days later, there was a recurrence of partial continuous epilepsy, followed by profuse vomiting and pneumonia Twenty-five days after admission, convulsions recurred and there was a gradual regression to a neonatal type of behaviour as shown by reappearance of rooting, sucking and tonic neck reflexes Again there appeared a fine tremor of the hands, lips and tongue with rigid legs Progressive deterioration was accelerated by a right hemiplegia following convulsions a few days before death (Consent for autopsy was not obtained)

(ii) A girl of 2 years 3 months born normally on 20 2 50 She is an only child of healthy parents with a neuropathic family history There was no history of convulsions and no illness except whooping-cough, in November 1951 The attack of pertussis pursued a normal course, but during convalescence, her mother noticed an unsteadiness of gait and a tendency to throw the right leg out when walking The mother compared this to the child's first attempts at walking at the age of 14 months She had been walking quite normally for several months before the illness When examined on 23 4 52, she was an apprehensive child who walked with a markedly unsteady gait with help No other abnormality was noted During the next few weeks, the ataxia increased and the child was finally unable to stand, and, owing to the tremor of her arms and hands, unable to feed herself C S F was normal

MUMPS

Encephalitis, myelitis, peripheral neuritis and labyrinthitis have been described, but the commonest complication is probably mumps meningo-encephalitis

Henderson (1952) notes the increasing frequency of central nervous system involvement in mumps during the last forty years. The criteria of involvement vary from observer to observer, and, quoting various authors, he shows that neurological complications vary from 1.35 to 66 per cent. In some instances the diagnosis was made on clinical grounds alone, and in others examination of the C.S.F. provides the only evidence. Complications are more frequently seen in epidemics, and preceding or concurrent salivary gland involvement or orchitis is not necessary to the development of complications.

Kravis, Sigel and Henle (1951) state that early serologic diagnosis appears possible in about two-thirds of cases of mumps meningo-encephalitis without salivary gland involvement. In 74 patients they note predominantly meningeal signs in 62.8 per cent., encephalitic signs in 15.7 per cent. and mixed signs in 21.5 per cent. Of 81 cases, 38 had no involvement of the salivary glands. Cases with and without gland involvement appear to be approximately equal. In the latter group, no clue is afforded unless there is a history of exposure to mumps or the consequent development of mumps in contacts.

In the series of 14 patients described by Henderson (1952) 11 had mild meningitis, and 4 of these 11 patients had no evidence of parotitis. In the majority of cases, vomiting, headache and feverishness are the cardinal symptoms, and common findings are drowsiness, stiffness of neck, abdominal pain and irritability. Less frequently backache and photophobia are described, and occasional instances of cerebral and cerebellar involvement have been noted.

Sequelæ are said to be rare, but Kravis, Sigel and Henle (1951) mention definite personality changes in one child three weeks after mumps meningo-encephalitis. Another child developed a left hemiparesis, a third mentally retarded child had a residual spasticity, and an 18-months-old child had ocular muscle palsy and dysphagia. Deafness, resistant to treatment, may be a sequel. All cases showed an increase in C.S.F. protein.

CASE REPORTS.—(i) A boy of 7 years was admitted into hospital on 1.12.50 with headache, backache, dysuria and feverishness. On examination there was photophobia, neck rigidity, a positive Kernig sign and an external squint of the right eye. No other abnormal feature was noted and there was gradual improvement. C.S.F. showed 140 mgm. per cent. of protein, 1700 cells (50 per cent. lymphocytes, 50 per cent. polymorphs), increased globulin, sugar 46 mgm. per cent. and chlorides 730 mgm. per cent. He made a complete recovery. His female sibling developed mumps one day after the boy's admission into hospital during a local mumps epidemic.

(ii) A boy of 8½ years was seen on 22.10.51 with a history of meningitis in May 1949, shortly after his elder sib had developed mumps. During the attack of " meningitis " he had periods of unconsciousness for the first few days and was bedridden for one month. After this attack, his mother thought he was stupid and would take no notice of remarks and requests. He was incontinent of urine and fæces from October 1949 and was increasingly dull and backward at school. He had developed normally in infancy and early childhood but had received a severe emotional shock by the death of his father three years previously Psychiatric investigation showed mental defect and personality change

CONCLUSION

The present series of cases appears to corroborate previously expressed views (Underwood, 1935, Henderson, 1952) that the incidence of neurological complications of infectious disease is on the increase It also seems to confirm the impression that complications tend to follow an epidemic of poliomyelitis In 1950, 29 cases of poliomyelitis were notified in the county with the peak of the epidemic in September Neurological complications of infectious disease appeared in December 1950 and reached a peak in February 1951, a total of 8 cases having been seen during this period

Although influenza is not a notifiable infectious disease, there was a particularly severe epidemic during January 1951 Where there is a neuropathic tendency the role of infectious diseases, particularly measles, in the ætiology of encephalomyelitis, cerebellar ataxia, and dementia in early childhood appears to be important, calling for modification of measles by gamma-globulin or convalescent human serum, in infancy and early childhood In view of considerably greater risk of encephalopathy following whooping-cough, immunisation of the infant is desirable

While neurological complications are, on the whole, rare, their manifestations are more harrowing and the end results often no less distressing than those of the more commonly recognised complications

REFERENCES

BYERS, R K, and MOLL, F C (1948), *Pediatrics*, 1, 437

BULLOWA, J G M, and WISHIK, S M (1935), *Amer Journ Dis Child*, 49, 923

FORD, F R, and WILSON, R E (1927), *Bull Johns Hopkins Hosp*, 40, 337

FORD, F R (1928), *Ibid*, 43, 140

FORD, F R, and GUILD, H (1937), *Ibid*, 40, 192

FORD, F R (1944), *Diseases of the Nervous System in Infancy, Childhood and Adolescence*, 2nd Edition, Springfield, Illinois

HENDERSON, W (1952), *Lancet*, 1, 386

KRAVIS, L P, SIGEL, M M, and HENLE, G (1951), *Pediatrics*, 8, 204

MALAMUD, N (1937), *Arch Neurol and Psychiat*, 38, November

MALAMUD, N (1939), *Ibid*, 41, May

MILLER, R, and DAVIDSON, J A (1914), *Brit Journ Child Dis*, 11, 15

SKOOG, A L (1920), *Journ Amer Med Assoc*, 74, 1697

SMITH, D C W (1926), *Amer Journ Dis Child*, 10, 445

TURNBULL, H M, and MACINTOSH, J J (1926), *Brit Journ Exper Path*, 7, 181

UNDERWOOD, E A (1935), *Brit Journ Child Dis*, 32, pp 83, 177, 242

WINNICOTT, D W, and GIBBS, N (1926), *Ibid*, 22, 107

NEW BOOKS

℞ *for Medical Writing* By E P GORDON, M D , and W C SHEPHERD Pp viii + 112, with 26 figures London W B Saunders 1952 Price 12s 6d

This manual makes no pretence to imitate the many excellent books on English composition, grammar and style, but it aims at assisting medical writers in the preparation of their papers It is an interesting and practical guide First it deals with the first, second and third drafts of a paper and with the corresponding revisions, with the beginning and end of the article and with special problems There is an excellent account of the subject of illustrations which shows how to make the most of the material available A long chapter discusses in simple fashion statistics employed in medical papers and points out numerous pitfalls Lastly, there are some useful appendices, including one which gives the accepted proof reader's conventional signs

This is a curiously omnibus booklet, but very readable and full of valuable advice, and it should be studied by all who aim at making a contribution to medical literature

A Handbook of Diseases of the Skin By H O MACKEY, F R C S I , L R C P I , D P H , L M , F R I A M Pp 216, with 36 illustrations Dublin C J Fallon 1952 Price 7s 6d net

The price of this book will appeal to students, the binding is good and the print is clear, but unfortunately the black and while illustrations fall far short of this high standard There is a discursive section on the commonly neglected subject of Industrial Dermatitis which should prove helpful to the student, on the other hand he is not likely to appreciate the amount of space devoted to rarities at the expense of some of the common conditions Few Dermatologists are likely to approve of the frequent recommendations to apply sulphonamide lotions and ointments Many will be puzzled by sentences such as —" *the* Senear-Usher Syndrome is generally regarded as a comparatively benign type of pemphigus about 90 per cent of all cases end fatally , in a week or ten days in acute cases, in chronic cases may be over some years "

Despite its many good points the book in its present form is unlikely to replace any of the existing " favourites "

A Synopsis of Neurology By TATLOW, ARDIS and BICKFORD Pp 523, 84 illustrations Bristol John Wright & Sons Ltd 1952 Price 30s

This book contains much information for its size Although synoptic in style it is easily read because of the use of many headings and variations in type The comprehensive section on neuro-anatomy and embryology emphasises their importance in an understanding of neurology The illustrations are good As a means of rapid revision and reference the book fulfils its purpose admirably

Annals of Physical Medicine Vol I, No 1 Edited by HUGH BURT Pp 36 illustrated London Headley Brothers January 1952 Single copies 6s each, Annual subscription 21s

This is the first number of a new quarterly, the official publication of the British Association of Physical Medicine (founded 1943) Physical Medicine is as old as the profession, but it is only within recent years that it has been set on a secure scientific foundation The new journal is to include all physical agents employed in diagnosis and treatment, and will deal with rehabilitation and resettlement and include the Spas and Health Resorts

There are two original articles in this first number The first is a well-planned investigation into the effects of microwaves (below 30 cm) The second is an account of a simple method of dealing with the resistant complications of varicose veins A useful feature of the journal is a collection of Abstracts of World Literature

This new periodical should meet an urgent need, and we wish it all success

The Neuroses By WALTER C ALVAREZ, M D Pp 667 London W B Saunders 1951 Price 50s net

This book, the product of extensive experience of the Neuroses, is written by a non-psychiatrist essentially for the benefit of non-psychiatrists The author, Professor of Medicine, Emeritus at the Mayo Foundation, has compiled an interesting and entertaining case book It is conveniently classified and well set out, so that a reference to almost every branch of medicine is readily available

While the scope of the book makes it difficult to allow a profound analysis of the vast numbers of problems which the writer tackles, his observations and advice are invariably experienced and practical

It is in no sense a textbook, rather, it may be read with profit and enjoyment by the already knowledgeable to pass the idle hour

The excellence of the paper and printing is especially noted, within what is not now regarded as an unreasonable price

Psychiatry in General Practice By C A H WATTS, M D, D OBST R C O G, and B M WATTS, M B, B S Pp xiii+228 London J & A Churchill, Ltd 1952 Price 12s 6d net

This is an excellent attempt to interest the general practitioner in some of the problems concerned with the diagnosis and treatment of psychological disorders A strong plea is made for the reorganisation of the general practitioner's time so that more attention should be given to this type of case, and it is pointed out that much time will be saved if fewer placebos are prescribed A number of case histories are satisfactorily described so as to illustrate points at issue The book should act as a stimulus to other general practitioners to follow in the footsteps of the Watts, and it can be recommended

Portrait of a Surgeon John Hunter By ERNEST A GRAY Pp x+219, illustrated London Robert Hale 1952 Price 16s

The author will already be known by his earlier books—*Surgeon's Mate* and *Man Midwife*—as a sympathetic writer on medical subjects

An excellent account is given of the life of Hunter, his work and his times, and the background is filled in with a description of the London of his day and details of his associates and pupils Full value is given to the aims and importance of Hunter's research work His observations forecast man's place in nature, and Darwin got much help from his publications The basis of Hunter's tremendous amount of work is summed up in a letter to his old pupil, Jenner—" Why think ? Why not try the experiment ? " To John Hunter is due a great part of the advance in medical knowledge that has taken place in the past 150 years, the man " who quickened into a science the dry bones of an archiac trade "

Familiar as is the life of John Hunter to many of us, the author has succeeded in painting a portrait that will be a joy to all

Pathology of the Fetus and the Newborn By EDITH L POTTER Pp xvii+574, 601 figures London Interscience Publishers 1952 Price 150s

Dr Edith Potter has a world wide reputation and immense experience in her subject, and this remarkable book is to a large extent a record of her personal, first-hand observations This gives it a pleasant freshness and impressive authority It is lavishly illustrated with admirably reproduced macroscopical photographs and photomicrographs Particularly striking are the descriptions and pictures of malformations, of which it contains an astonishing and probably unique collection This occupies much of the book, but other aspects of the subject are not neglected, and there is much useful information about diseases and injuries, prematurity, placental pathology and various general problems The author's interest in the clinical aspect of the subject increases the value of the book for obstetricians and pædiatricians as well as for pathologists It is a very important contribution to the literature of fœtal and neonatal pathology, and much the most complete and authoritative work on this subject at present available

Osler—The Man and the Legend By W R BETT, M R C S, L R C P Pp vi+125, with 7 photogravures London William Heinemann 1952 Price 15s net

The author points out that Harvey Cushing's *Life of Sir William Osler* must remain the standard reference on all things Oslerian, although it fails in many ways to convey the spirit of Osler to those who knew him not He, therefore, makes a new approach to the subject and portrays and interprets Osler in some dozen aspects which are common to him and to those to whom he is only a legend The picture is largely built up by extracts from Osler's own writings laced together with some detail of his medical career

One of the most striking things to which the author draws attention is the changing character of medical practice Osler laid enormous emphasis on the study of typhoid fever and pneumonia, scourges which have largely disappeared He prophesied that in a generation the mortality from tuberculosis would be reduced by 50 per cent Aneurysm of the aorta, so important in his day, has become a rarity, on the other hand, a vast increase has occurred in the incidence of coronary disease Osler said he had reached his Fellowship before he saw a case of angina pectoris, and he pointed out that in his series there were more doctors than members of any other profession, so that the disease might almost be called " morbus medicorum "

There are chapters on Osler as medical historian and classical scholar, as bibliophil, and on many other aspects of his life

This little book is in no sense a full biography, but it does give an attractive picture of the man It is delightfully written and exceedingly interesting, and well worth the attention of the medical profession

Scoliosis By SAMUEL KLEINBERG, M D Pp xvi+286, with 163 illustrations London Bailliere, Tindall & Cox 1952 Price 57s 6d net

Kleinberg's textbook on Scoliosis, first published in January 1926, has now been completely re-written—and of necessity, as so many changes have taken place in many aspects of the condition He aims to present the modern concept of the pathogenesis, to elaborate the etiology, and to review the results of modern methods of treatment

In discussing the etiology, the author states that his careful study has revealed that 25 per cent are hereditary, and suggests it to be one's duty to inform a man or woman with scoliosis that their children may also be so afflicted He does not say much about mensuration, because he does not believe that an involved method of graphic recording of a scoliotic deformity has any real practical value The chapters on treatment are comprehensive and many braces and jackets are fully described, but one would like to have had more definite indication of the author's perference In speaking of conservative treatment the author says no cure of a structural scoliosis has been reliably reported and that 10 to 20 per cent require operative treatment, from which it is suggested that in the remaining 90 to 80 per cent conservative treatment is satisfactory Kleinberg recommends unilateral spine fusion of the Hibbs' type on the concave side with a beef bone graft to reinforce the fusion The beef bones are obtained from the hospital kitchen They are boiled for one hour, then cut to suitable lengths, and stored in 70 per cent alcohol where they will keep indefinitely

This is an interesting and provocative book, but the illustrations and general production are not up to the best standards in this country

Essentials of Neurosurgery By LESLIE C OLIVER, F R C S Pp viii+198, with 50 illustrations London H K Lewis & Co 1952 Price 25s net

This concise book is the first of its kind to be published in the country, and represents a broad survey of the present trends in neurosurgical practice It will be of especial value to the post-graduate who has embarked upon his general surgical training and has the higher examinations before him For the undergraduate it will form an introduction to the rapidly widening field of neurological surgery

NEW EDITIONS

Forensic Medicine By KEITH SIMPSON, M D Second Edition Pp viii+344, with 131 illustrations London Edward Arnold & Co 1952 Price 21s

This book has the merit of comparative brevity, and the author's direct style makes it easy to read Legal and technical aspects of the subject are dealt with only in outline, and for this there is much justification in a volume intended primarily to meet the needs of students and general practitioners It does more than this, however, for it conveys in a precise and unequivocal manner the author's considered views on points both controversial and otherwise These views reflect an extensive practical experience, independent thinking and sound common-sense, all of which enhance the interest and value of the book The illustrations, with few exceptions, are very good, and the production is excellent

Tuberculosis of Bone and Joint By G R GIRDLESTONE and E W SOMERVILLE Second Edition Pp xii+314, with 182 illustrations London Oxford University Press 1952 Price 45s net

The second edition of this well-known monograph describes the old and well-tried surgical principles of Owen Thomas and Jones for the treatment of skeletal tuberculosis It rightly states that they are the bed rock of treatment, but it is depressing that our patients have still to look forward to such long periods on their back, though it is hoped that chemotherapy may shorten this considerably Chemotherapy is very briefly dealt with because the authors believe it too early to judge of results Little is said of the latest inventions, new theories, or experimental work This can be judged in reading of the frequency of bacillæmia in human tuberculosis since the references—two—are twenty years old Local excision of minor degrees of infection, with decompression, is used in many Clinics now under an antibiotic cover but is not mentioned here, though where a large area of bone is infiltrated wide excision is advocated, its justification being a better prognosis and a much quicker propsect of recovery

The book, which is very well produced, forms a useful basis for study for those taking up this surgical speciality

Emergency Surgery Part IV By HAMILTON BAILEY and NORMAN M MATHESON Sixth Edition Pp iv+193, with 311 illustrations Bristol John Wright & Sons Ltd 1952 Price 21s net

This publication continues the production in five separate parts of a new edition of this popular work The text has been extensively revised and many of the illustrations, already a distinctive feature, have been improved

Progress in Clinical Medicine By various authors Edited by RAYMOND DALEY, M A, M D, M R C P, and HENRY G MILLER, M D, M R C P, D P M Second Edition Pp xi+426, with 43 illustrations London Messrs J & A Churchill 1952 Price 30s

This book was first published in 1948 and its popularity necessitated a reprint in the same year In the following three years the editors decided, in view of the rapid advances in medicine, to enlarge and rewrite the book completely, each subject remaining the work of a known authority Wisely, the advances discussed are limited to what are now established medical and surgical practices in hospitals The surgical contribution, especially in the fields of respiratory, neurological and psychiatric diseases, is timely, and covers ground often unfamiliar to the general physician

To the practitioner and specialist there is no comparable work available so excellently produced at so low a cost

The Premature Baby By V MARY CROSSE, O B E, M D, D OBSTET, R C O G Third Edition Pp 181, with 18 illustrations London J & A Churchill Ltd 1952 Price 16s net

The appearance of the third edition of this now well-known book is ample evidence of its popularity and acceptance as an authoritative work It has been carefully revised and brought up to date with some additions

Not only is the book full of detail but it also includes many useful references to the literature

Textbook of Histology By A A MAXIMOV and W BLOOM Sixth Edition Pp x+616, with 986 illustrations, 257 in colour on 580 figures London W B Saunders & Co 1952 Price 50s

This edition has been extensively revised, and a new introductory chapter has been written, correlating the submicroscopic, biochemical and enzymatic constitution of cells with their structure and function This chapter will be found most helpful to the student

The chapter on the connective tissues has been advantageously re arranged to include the materials dealing with inflammation and repair

The section on the Endocrine Glands has been completely re-written and a separate chapter devoted to each gland Many new illustrations have enhanced the value of this section

Further important additions include forty-six new photomicrographs and several excellent illustrations by phase contrast

The author relies chiefly on drawings for the illustrations, and it is felt that a large number of these could be replaced by photomicrographs with advantage to the student, especially if they were up to the standard of those included from the atlas of Herrath and Abramov

The student will find this book easy to follow and very moderately priced for its size

BOOKS RECEIVED

Edited by MACBRYDE, CURIL MITCHELL, A B, M D, F A C P Signs and Symptoms Second Edition	(*Staples Press Limited, London*)	70s net
HOLZMANN, Dr MAX Clinical Electrocardiography	(*Staples Press Limited, London*)	105s net
SNYDER, EUGENE F, M D From a Doctor's Heart	(*Philosophical Library, New York*)	$3 75
SWIET, JOHN DE, M D (LOND), M R C P Essentials for Final Examinations in Medicine Fourth Edition	(*J & A Churchill Ltd, London*)	12s net
WOLSTENHOLME, G E W, O B E, M A, M B, B CH Ciba Foundation Colloquia on Endocrinology	(*J & A Churchill Ltd, London*)	35s net
Edited by BIRCH, C ALLAN, M D, F R C P Emergencies in Medical Practice	(*E & S Livingstone Ltd, Edinburgh*)	32s 6d net postage 1s 1d home
Edited by COPE, V ZACHARY, B A, M D, M S (LOND), F R C S (ENG) Medicine and Pathology	(*Her Majesty's Stationery Office, London*)	50s net
MCLAGGAN, J DOUGLAS, C V O, F R C S, and COLLIER, JOSEPHINE, F R C S Diseases of the Ear, Nose and Throat Second Edition	(*H K Lewis & Co Ltd, London*)	37s 6d net
WILLIS, R A, M D, D SC, F R C P The Spread of Tumours in the Human Body	(*Butterworth & Co (Publishers) Ltd, London*)	63s net
LAW, W ALEXANDER, O B E M D, F R C S Osteoarthritis of the Hip	(*Butterworth & Co (Publishers) Ltd, London*)	25s net by post 1s extra
LANGDON DAVIES, JOHN Westminster Hospital 1719 1948	(*John Murray, London*)	21s net

Edinburgh Medical Journal

November 1952

THE INFLUENCE OF RECENT ADVANCES IN LEPROSY ON PRESENT-DAY CONCEPTIONS OF THE DISEASE IN RELATION TO ITS DIAGNOSIS, TREATMENT AND PREVENTION

By R G COCHRANE, M D, F R C P, D T M & H

INTRODUCTION

THERE may be many who consider that the emphasis which I place on recent work undertaken in Bombay unsound, for they will charge me with building up a theory on an edifice whose stability is by no means proven I accept this charge, but I believe that the basis of this theory is logical, and proof will not be forthcoming until workers are willing to put as much time, care and patience into confirming Khanolkar's recent work as he himself has done Others will say that leprologists have not, as yet, accepted these findings My reply is that without the help of careful research workers in fields other than leprosy it is impossible to get a true picture of the disease For too long leprosy has been in a compartment by itself, surrounded by an atmosphere of pity and even of sanctity, which has prevented it being viewed as an ordinary malady, the complete elucidation of which cannot be achieved without the help of scientists in all fields Leprosy, therefore, must be studied in relation to disease processes as a whole An explanation of related phenomena in other fields would add to our knowledge of this disease which has baffled mankind for many decades Compassion and pity must be shown to those who are unfortunate enough to be chronically ill, but to select one disease as a particular manifestation of Divine disfavour is to distort the picture and hinder research Disease is a manifestation of a disordered body and a disordered world, and every influence—mental, physical and spiritual—which enables a man to achieve health must in these days of enlightenment be welcomed

An address delivered to the Edinburgh Branch of the Royal Society of Tropical Medicine, on 4th March 1952

DIAGNOSIS

The controversy as to whether the *M lepræ* is the causative organism of leprosy was sharpest in the latter part of the last century The *M lepræ* has now been accepted as the specific cause of the disease, and this evidence has been greatly enhanced by the development of modern techniques The latest worthy of mention are the Fite-Farraco method of staining acid-fast bacilli in the tissues, and the recent concentration method for the examination of tissue from leprosy patients devised by Khanolkar of Bombay The former method is brought to the attention of histopathologists in staining sections for acid-fast bacilli, the latter method can be used in any well-equipped laboratory This consists of taking a piece of tissue approximately 5×3×5 mm from the selected area of skin in the person diagnosed as suffering from leprosy, placing the tissue in 3 c c of 1 per cent acetic acid for two to four hours This enables the epidermis to be peeled off, leaving the corium intact

The tissue free from the epidermis is dropped into a pyrex glass homogeniser tube with an inner ground-glass surface, in 3 c c of 1 per cent acetic acid The tissue is crushed at about 2000 r p m with an electrically operated mechanical glass crusher for about five to ten minutes The crushing process is continued until a homogeneous milky emulsion of the tissue particles is obtained and a residual flake of the tough dermal tissue sinks to the bottom of the tube The tissue particles adhering to the sides of the stirrer and the tube are washed down with about 1 to 2 c c of 1 per cent acetic acid, and the contents are brought to a total volume of 5 c c Twenty drops of petroleum ether-sulphuric ether mixture (1 in 10) are added to the turbid fluid with a drop bottle The tube is shaken vigorously for a few minutes to ensure a thorough mixing of the tissue suspension and the ether mixture The tube is then corked and allowed to stand in a test tube rack for about fifteen to twenty minutes

Ten c c of distilled water are let into the tube along its sides for washing down any particles adhering to the wall of the tube After about two to five minutes a white or amber coloured ring is formed on the surface which is quite distinct from the subjacent liquid This layer contains the micro-organisms caught up by droplets of petroleum ether Eight drops are carefully picked up from this layer with a sterile 3 mm platinum loop and deposited on a clean glass slide The next eight drops are placed on another clean slide The drops are then spread over an area roughly 2×2 cms The slides are kept in a covered petri-dish to protect the smears from dust and allowed to dry in an incubator at 37° C The dried smears are fixed by flooding the slides with Carnoy's fixative and leaving it for fifteen minutes The fixative is then poured off and the smears are dried in air in the usual manner Full detals of this method will be published shortly It is now possible to say that if one or other of these techniques is used acid-fast bacilli can be isolated from every active case of leprosy I may say, in passing, this raises the question in a more acute form of the infectivity of what has hitherto been described as non-infective leprosy I, personally, do not believe this work alters the still generally accepted view that leprosy is only infective in those cases where bacilli can be discovered *by standard methods of examination* To find an occasional baccilus after prolonged search, and after crushing the whole tissue, hardly justifies the opinion that the case is infective

It is quite true that the presence of *M lepræ* is not necessary to make a diagnosis of leprosy Nevertheless, it is always a source of satisfaction if the acid-fast organism can be detected either in sections or from the tissues It may be asked whether these methods can be adopted in cases in which the disease has to be diagnosed where the only sign is anæsthesia, particularly in the areas of the distribution of the peripheral nerves All that can be said is that while methods to find bacilli in such cases involve complicated techniques—*e g* nerve biopsy—any active case of anæsthetic leprosy (polyneuritic of the Havana classification) which has been studied up to the present has shown the presence of *M lepræ* either in the exudate around the nerve, or in the nerve itself

Ever since the discovery of the *M lepræ*, and before this significant event, leprosy has been divided into two distinct types—that which has predominantly neural signs, and in which bacilli are seldom found by standard methods of examination , and that in which neural signs are less evident, and bacilli are found, frequently in large numbers

Gradually, as the clinical picture was built up—and this was the result of patient observations of many workers—it was realised that all lesions of leprosy could be separated into those which showed a positive tissue immunity, and those in which the tissues appeared to welcome the *M lepræ* and made no attempt to check its multiplications Thus two distinct types were differentiated—one showing a positive lepromin reaction and the other a negative one While it is impracticable to base a classification of leprosy on immunological data alone, it is becoming apparent to an increasing number of workers that the tissue response is the clue to the understanding of the protean clinical manifestations of the disease The diagnosis of leprosy is now no longer just a matter of whether a patient has leprosy or not, but the type of leprosy, its course, its response to therapy, or its regression with or without treatment, are factors which all have to be taken into account in the intelligent management of a case presenting itself to a physician for diagnosis

The South American workers were the first to maintain that the lepromin test must be taken into consideration in any classification of leprosy which endeavours to be complete These workers pointed out that all leprosy can be divided into that which shows a positive lepromin—tuberculoid or lepride—and that which shows a negative response—leproma There has, however, been considerable confusion in the matter of the tuberculoid picture, because in addition to those lesions which are positive to lepromin, and those which are negative, there are certain cases which show a variable lepromin These are sometimes difficult to diagnose and classify It is becoming increasingly accepted that this group of lesions, variously described as border-line (Wade), (Lowe), intermediate (Cochrane), dimorphous (Khanolkar), reactional tuberculoid (Schujman), and, more recently, exclusively localised macular lesions (Dharmendra), are a clinical entity whose behaviour and evolution can be predicted, and which must be included in any modern classification of the disease The histological characters of these lesions and their immunological response were described by me some years ago In the recent Pan-American Conference I placed before that meeting the suggestion that the classification of leprosy should be based on the immunological response of the tissues The following is the suggested modification of previous classifications, which I feel may lead to a more logical division of the various clinical manifestations which have been described

I am not as yet sure, but from evidence which is being collected it appears that all lesions, whether macular, infiltrated or polyneuritic, divide themselves into one or other of the above groups It may be that in the dimorphous or intermediate group of cases, macular, as well as the polyneuritic lesions, will ultimately be differentiated

Lepromin Positive	Lepromin Variable	Lepromin Negative
(Tuberculoid)	(Dimorphous or Intermediate)	(Leproma)
Maculo anæsthetic		Preleproma
Minor lepride	Atypical lepride	Macular leproma
		Diffuse leproma
Major lepride	Atypical leproma	Infiltrating leproma
		Nodular leproma
Polyneuritic		Polyneuritic

For the accurate assessment and diagnosis of a case of leprosy it is inadequate simply to confirm the presence or absence of the cardinal signs of the disease—loss of sensation, tactile or thermal—nerve enlargement—or the presence of acid-fast bacilli in the tissue In order to give a correct opinion with reference to diagnosis, response to treatment, etc , both the lepromin test and tissue biopsy, I believe, are essential Admittedly, under conditions in the tropics, this is not possible in all cases Nevertheless it must be accepted that without these aids one cannot be wholly satisfied that the best is being done for one's patients Further, as experience accumulates, our clinical assessment becomes more accurate when it has been based on a long study of histopathological material from a large number of cases of leprosy I believe that to decry these methods as time-consuming and impossible only results in a superficial judgment, and does not encourage that detailed investigation which alone stimulates scientific research into all aspects of the disease

THERAPY

I shall now pass on to the consideration of therapy in the light of the observations which I have just made In a recent address before the Royal Society of Tropical Medicine in London I placed before the meeting a suggestion of the method of action of the sulphone drugs These drugs possibly act by causing the tissue environment to become unfavourable to the multiplication of *M lepræ*, and under these adverse conditions morphological changes take place in the bacilli, which become reduced to the granular form, and, over a period of two to five years or more, gradually disappear from the tissues but remain for considerably longer in the subcutaneous nerves

There has been not a little discussion as to the active principle of the sulphone preparations, and the majority consider that all sulphones are effective in proportion to the amount of free DDS available In other words these persons hold that there is no reason for giving complicated proprietary derivatives of DDS when all that happens is that these are changed to the parent sulphone, either in the body or by virtue of the fact that in the finished product free DDS can be demonstrated as an impurity Others believe that the insistence on the parent sulphone being the main active agent may not altogether be true and there is growing evidence to show that di-substituted sulphones, given parenterally, are partially, and may be largely, converted into a mono-substituted derivative

A point which is of importance, and will be dealt with in connection with the discussion on prevention, is the length of time sulphone therapy should be given The fact that granular forms of the bacilli can be found in nerve tissue as long as eighteen months after a patient has been negative to standard methods of examination indicates that caution must be the watchword in any decision to stop sulphone therapy Now that the generally accepted dosage of the sulphones is very much lower, it can be stated that patients should continue a maintenance dose of sulphones (1 gm of sulphetrone parenterally, or 300 mgm DDS—these dosages are given, preferably, twice weekly) for at least two years after they have been declared negative

While it cannot be said that the sulphones satisfy the conditions of a certain specific for leprosy, the tendency to alter treatment because improvement is not rapid enough must be deprecated It should be remembered that while the clinical response is dramatic, the bacteriological response is very slow, and only begins definitely to be seen after the second or third year of treatment There is a place for other remedies—*e g* Thiosemicarbasone—in leprosy, but in the therapeutics of leprosy pride of place must be given to the sulphone preparations, until a better drug is discovered Unless there is intolerance to the sulphones, treatment should not be changed, where there is manifest intolerance, particularly on low dosages, then one of the Thiosemicarbasones should be administered There is sufficient accessible literature to help the physician decide the form of sulphone therapy suitable to his patients in the conditions under which he is working

One matter, however, should be mentioned, and that is reaction in leprosy This divides itself into three separate categories —

1 Violent local tissue response
2 Erythema nodosum, or acute lepra reaction
3 Sub-acute, or chronic, lepra reaction

The first is seen in the leprides, or tuberculoid cases I personally believe that sulphones act in tuberculoid cases by virtue of the fact that they cause the bacilli, in the early stages, to multiply, and this sets off the trigger which results in an acute tissue response Because of this reaction resolution of the disease is more rapid, and, thus, sulphones hasten the recovery of the patient The speed of the recovery is in direct proportion to the intensity of the reaction It is because of this capacity to set up reactions in the leprides that care must be taken lest increased nerve damage is produced, with resultant severe deformity It is, therefore, sometimes advisable to excise the nerve sheath, in those cases which show gross enlargment of the nerve with œdema and tenderness, before sulphone therapy is started

The reaction in the leprides, and to some extent in the dimorphous lesions, is an acute antigen antibody response seen locally in the tissues Because of this localised response in tuberculoid leprosy some lesions may flare, while others are quiescent In other words the antigen—the bacillary products—is localised in the tissue

In the second form of reaction—erythema nodosum leprosum—the mechanism of the response is different and the approach to its control must be along other lines This, too, is an allergic phenomena, but the antigen—bacillary products—is no longer confined to the tissues, but is circulating and as a result of the rapid multiplication of the *M lepræ* and its equally rapid destruction, a hypersensitisation arises and high fever and erythema nodosum lesions are seen The tissues themselves are not sensitised, but there is a humoral response to the bacillary products—that is to say erythema nodosum is a type of Herxheimer reaction and comes under Stokes' definition of a toxi-leprid In this connection I quote from *Fundamentals of Medical Dermatology*—" It is probable that the toxi erythemas, erythema multiforme as well as erythema nodosum in its various forms can be explained on an ' id ' basis, associated with central, local or blood stream infection " The failure to understand the mechanism of these two different allergic phenomena gives rise to much confusion

It is interesting to note that cortisone or A C T H in relatively small doses, 50 mgm per day, appears to control erythema nodosum and permits the continuance of sulphone therapy More recent information from Lowe in West Africa, however, suggests that this form of treatment should be of short duration, lest the disease itself be aggravated The other form of reaction, where there is rapid multiplication of *M lepræ* without corresponding destruction, is much more serious and indicates the necessity for the immediate cessation of sulphone therapy, and its very gradual resumption when the acute phase has passed In such cases even as small a dose as 25 mgm twice a week of DDS may be too great

PREVENTION

In the light of modern knowledge of leprosy the question of control of the disease must be considered The main basis of all control must still be the separation of infected cases from healthy persons, particularly children The futility of complete and compulsory isolation has frequently been demonstrated These measures arise from a primitive fear of the disease and only encourage false notions as to the infectivity of leprosy Neither is it useful or practical to depart from the accepted opinion that the only case which is a serious public health problem is the open case On the other hand, in our present state of knowledge, it would seem to be a serious form of wishful thinking to believe that the granular forms of the bacilli are innocuous, and dying or dead So long as acid-fast granules can be found, the case should be classified as potentially infective When it is realised that from the time of infection with *M lepræ* to full development of active infective lepromatous leprosy may be a matter of twenty years or more, and if, as one has seen, under sulphone therapy the lesions gradually pass through the phase of resolution back to the pre-leproma stage, it seems not unreasonable to conclude that if sulphone therapy is discontinued it may take as long a period for a relapsed case to return to the frank lepromatous type This does not mean that sulphone therapy is not a powerful aid in controlling leprosy, it does mean that it is dangerous to rely on therapy to stem the epidemic of leprosy, and that control must be accompanied by partial, but not necessarily compulsory, segregation Any campaign which bases its main line of attack on mass treatment by sulphone therapy, without adequate facilities for segregation of the open case, may lead to gross disappointment, and, further, the results of such facile optimism may not be seen for many years Therefore, while encouraging the widespread use of the new and more effective sulphone remedies, which have now come within the economic reach of all, one must combat the tendency to think that victory has already been achieved A disease which has baffled us for so many decades is not likely to be easy of ultimate control The new and hopeful advances in our knowledge of therapy challenge us to still greater effort It is confidently hoped that, as a result of the combined activities of the epidemiologist, the pathologist, the clinician, and the orthopædic surgeon, leprosy, ere long, will be robbed of its terror, and be yet another of the scourges of mankind which have been vanquished

REFERENCES

" Classification of Leprosy " (1948), *International Journal of Leprosy*, **16**, 201

COCHRANE, R G (1940), *International Journal of Leprosy*, **8**, 445

COCHRANE, R G (1947), *Practical Textbook of Leprosy* Oxford University Press, p 76

COCHRANE, R G (1949), *Leprosy in India*, **21**, 86

COCHRANE, R G (1951), " Classification of Leprosy," Paper presented at the Pan-American Leprosy Congress, Buenos Aires (Not yet published)

COCHRANE, R G (1952), *Transactions of the Royal Society of Tropical Medicine* (In press)

DHARMENDRA, MURKERJEE, N and CHATTERJEE, S N (1951), *Leprosy in India*, **23**, 200

FITE-FARRACO (1948), From LILLIE, R D , *Histopathological Technique*, Blakiston, Philadelphia, p 217

KHANOLKAR, V R , *A Method of Concentrating* M lepræ *from the Tissues* (In Press)

KHANOLKAR, V R (1951), Indian Council of Medical Research Special Report Series (No 19)

LOWE, JOHN (1936), *International Journal of Leprosy*, 4, 195

SCHUJMAN (1950), *International Journal of Leprosy*, **18**, 11

STEWART, A B (1933) *Leprosy in India*, 5, 183

STOKES, JOHN H and ASSOCIATES, *Fundamentals of Medical Dermatology*

WADE, H W , and LOWE, J (1937), *Leprosy in India*, **9**, 39

WADE, H W (1940), *International Journal of Leprosy*, **8**, 309

APPLICATION OF F 933 AS A ROUTINE TEST IN SUSTAINED HYPERTENSION

By DONALD F GIBBS, M B, M R C P E

From the Royal Infirmary, Edinburgh

ONE of the less common, but important, causes of hypertension is that due to the pheochromocytoma tumour of chromaffin tissues, important in that, if left alone the tumour can produce all the devastating complications associated with a high diastolic blood pressure, whereas, if discovered, removal of the tumour offers the unusual opportunity of curing the hypertensive subject

Pheochromocytomas, although rare, may well pass unnoticed Smithwick (quoted by Goldenberg *et al*, 1947) found that in 1000 hypertensive subjects, undergoing surgical sympathectomy, inspection of the adrenal glands revealed pheochromocytomas in 0 5 per cent, since at least 15 per cent of the tumours are extra adrenal the true incidence may well be higher, and several authors, notably Stout (1946) and Goldenberg *et al* (1947), point out that extra-adrenal pheochromocytomas are probably much more common than is generally recognised

The tumours may be associated with the classical syndrome of paroxysmal hypertension, vasoconstriction, pallor, headache, tachycardia, sweating and tense feelings in the epigastrium More commonly they present with persistent elevation of the blood pressure, indistinguishable from essential or malignant hypertension (Green, 1946) and without fluctuations of pressure (Binger and Craig, 1938, Palmer and Castleman, 1938, Philips, 1940, McCullagh and Engel, 1942, Kirschbaum and Balkin, 1942, Thorn, 1944)

Considerable amounts of adrenaline and also nor-adrenaline are produced in pheochromocytomas (Holton, 1949, Goldenberg *et al*, 1949 and 1950), but no other pressor agent has been isolated Release of adrenaline and nor-adrenaline into the circulation can produce hypertension At the present time the precise mechanism of the hypertension produced by pheochromocytomas is not clearly understood, although it appears to have an angiospastic basis and is generally reversible on removal of the tumour or tumours It seems likely that excess of these pressor substances over a period of time may set up some secondary mechanism of hypertension, which is not dependent upon the continued presence of these compounds for its maintenance (Calkins *et al*, 1950, Goldenberg *et al*, 1950) The mechanism of hypertension is discussed by Calkins and Howard (1951)

Work carried out during tenure of a Crichton Research Scholarship from the University of Edinburgh

Of the several tests suggested to simplify recognition of pheochromocytomas all can be divided into two groups The first consists of test substances, such as histamine and mecholin, which can produce a typical paroxysmal attack, and which are especially useful in subjects whose blood pressure is within normal limits between attacks The second group consists of agents which can block the effect of adrenaline and nor-adrenaline on the blood pressure, and which are especially valuable in those instances with sustained hypertension The most suitable of these for clinical use is F 933 (2, 1-piperidylmethyl-1, 4-benzodioxane) Although this substance was known to have adrenolytic actions and was first investigated by Fourneau and Bovet in 1933, it was not until 1947 that Goldenberg, Snyder and Aranow described its use as a clinical test Since then the drug has been fairly widely used in America but few reports are available in the British literature as yet

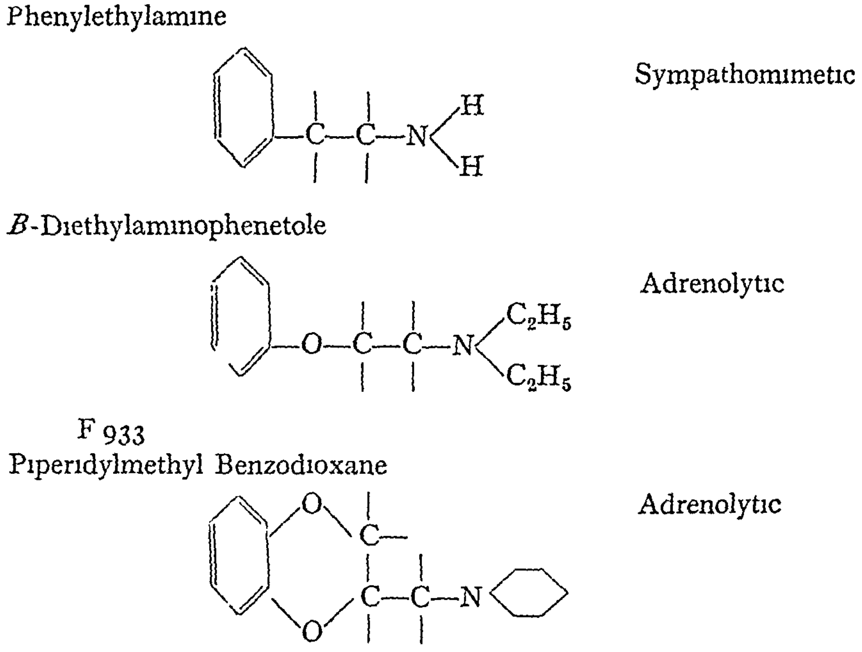

FIG 1 —The relation of F 933 to phenylethylamine

Figure 1 shows the relationship of F 933 to a simple sympathomimetic amine known as phenylethylamine The introduction of an oxygen atom between benzene ring and side chain results in the production of a substance with adrenolytic properties It was suggested that F 933 accelerated adrenaline inactivation (Morison and Lissak, 1938) Competition for alcohol-amine receptors and prevention of adrenaline and like substances from combining with these receptors has been suggested by Seed and Calkins (1949)

In suitable doses of approximately 0 25 mg per kg body weight, F 933 can abolish and reverse the action of adrenaline upon the blood pressure in animals (Fourneau and Bovet, 1933, de Vleeschhouwer, 1935, Bovet and Simon, 1937) and in man (Goldenberg *et al*, 1947)

Further, F 933 can counteract the pressor effect of nor-adrenaline in man (Goldenberg, 1950) to a greater extent than in animals (Stehle and Ellsworth, 1937) At the same time it does not antagonise the action of the sympathetic system upon the blood pressure unless administered in very large doses In addition, F 933 retains certain sympathomimetic properties such as stimulation of the central nervous system

On the basis of these actions, Goldenberg and his colleagues suggested that if hypertension is due to excess circulating adrenaline and nor-adrenaline, then it will be abolished or significantly decreased following intravenous injection of F 933 in suitable dosage, whereas if hypertension is due to any other cause, the blood pressure will not fall following such injection The former response of a fall in blood pressure following injection is referred to as a "positive" result, and the latter response of no fall in blood pressure as a "negative" result During a positive reponse the fall in blood pressure is generally sustained for ten to twenty minutes

A positive result in the absence of a pheochromocytoma has been reported in only one authentic instance (Dana and Calkins, 1949) and in this case a large cell neuroblastoma incorporating the left adrenal gland was found Claim to discovery of a "false" positive case was made by Taliaferro *et al* (1949) but cannot be considered authentic Grimson (1950) mentions a positive response in the presence of excess blood adrenaline in a uræmic subject in whom at autopsy no tumour could be found A negative response in the presence of a pheochromocytoma is reported in 3 cases quoted by Goldenberg *et al* (1950) Mason (1951) described 2 other such cases In such instances it is held that a secondary mechanism of hypertension has been set up The frequency of such false negatives is impossible to assess at the moment Thus, while a positive F 933 test almost certainly indicates the presence of one or more pheochromocytomas, a negative test does not certainly exclude a tumour

Prunty and Swan (1950) who carried out clinical experiments similar to those of Goldenberg *et al* (1947 and 1950) concluded that the mode of action of F 933 was complex and could not be explained as a simple blockage of adrenaline like substances Study of published work on the subject supports this view, but at the same time shows that there is evidence that F 933 is of great value in aiding recognition of pheochromocytomas as a cause of sustained hypertension, whatever its precise mechanism of action may be

Objections have been raised to the F 933 test on the grounds of unpleasant, alarming and dangerous effects by Drill (1949) in America, and such effects are stressed in a small series of cases reported in Great Britain (Prunty and Swan, 1950, Barnett, 1950) In a patient who had had hypertensive encephalopathy, features of encephalopathy similar to those previously experienced followed injection of F 933 (Green and Peterson, 1950) Swan (1951) successfully prevented a similar occurrence with tetræthylamonium bromide Wilkins *et al*

(1950) reported severe reactions to F 933 in 8 per cent of hypertensive patients

It is the object of this paper to describe the use of a simplified F 933 test and to comment especially upon the side effects experienced by the 400 subjects who received the drug

MATERIAL

Four hundred subjects received the standard test dose of F 933, 300 of these had sustained diastolic hypertension and of the remainder 43 had systolic hypertension associated with arteriosclerosis and a normal or slightly raised diastolic pressure, 22 subjects had thyrotoxicosis associated with a raised systolic pressure, and symptoms similar to those occurring in pheochromocytoma Ten subjects had anxiety states and were chosen on account of their apprehensive emotional nature, the remaining 25 were normal healthy individuals at the time of the test

Of the subjects with diastolic hypertension, 10 were in the malignant phase and 6 of this group had had recent hypertensive encephalopathies, the remaining 290 subjects had " benign " hypertension and 21 of this group had an acute progressive form of the disease Five of those in the " malignant " phase had had essential hypertension and 2 had had pre-eclamptic or eclamptic toxæmia of pregnancy, the others being probably of renal origin One hundred and seventy-five of the " benign " cases had essential hypertension, 64 were considered to be of renal origin and another 42 had been subject to pre-eclamptic or eclamptic toxæmia of pregnancy on one or more occasions, 2 had coarctation of the aorta and 5 were myxœdematous, 1 had an auditory neuroma, but died soon after its removal and its rôle in relation to the hypertension was uncertain, 1 young man had had poliomyelitis and also a doubtful renal history

The ages of the hypertensive patients ranged from sixteen to sixty-five years, the average being forty-six years This is lower than might be expected, but is explained in that all but 60 subjects were selected on account of the fact that they had developed diastolic hypertension at a relatively early age 76 were males and 224 were females The preponderance of the latter is partly related to the greater number of hospital beds available for women Of all the subjects, 7 of the diastolic hypertensives had been in left ventricular or congestive failure as had been 16 of the arteriosclerotic group The test was not carried out in the presence of uncontrolled cardiac failure Twelve subjects suffered from a moderate degree of angina pectoris and 10 others had healed myocardial infarcts, more than two and less than eight months old Six had early renal failure at the time of testing and 2 advanced renal failure

Four of the hypertensives had very labile pressures, and in 1 of these the diastolic level varied from 50 mm to 194 mm Two of these and

3 other hypertensives had histories suggesting the " adreno-sympathetic " syndrome

Seventeen of the hypertensive subjects have since died, including 5 of the " malignant " group, and autopsy inspection of the sympathetic chain and adrenal glands was thus available 1 subject mentioned, whose pressure was exceptionally labile, has had post-mortem examination carried out All had " negative " F 933 responses and in none were pheochromocytomas found

TECHNIQUE

The object of the test was carefully explained to each subject before the test began , each subject was instructed to report the onset of subjective sensations and also to note their disappearance The test was carried out in quiet surroundings, to which the subject was accustomed The blood pressure was estimated every two minutes over a period of twenty to forty minutes until a resting baseline was obtained with the subject lying comfortably in bed

The drug was made up in 2 ml ampoules containing 10 mg per ml in normal saline , samples from batches were checked by the manufacturers, Messrs May and Baker, and found to contain the correct proportion of F 933 The dose administered was 10 mg per square metre body area, and this was diluted up to 10 ml in normal saline immediately prior to use, the usual dose being in the neighbourhood of 16-18 mg

After the resting blood pressure had reached a satisfactory baseline, the test dose was injected by an assistant into a suitable arm vein The period of injection was two minutes in each instance During injection the blood pressure was estimated every thirty seconds and thence at minute intervals until it returned to the resting level, and then at two minute intervals for a further thirty minutes

Within one or two days the test was repeated under the same circumstances, using 10 ml of normal saline instead of F 933, a fact of which the subject was not aware at the time No other drugs were given at the time of the test save that phenobarbitone, ½ gr thrice daily, had been administered before and after the test to all the hypertensive and thyrotoxic subjects

RESULTS

1 BLOOD PRESSURE —*Hypertensive Subjects* —In no subject was there a clear " positive " response to the test In 250 instances there was a variable rise in systolic pressure of 10-72 mm generally beginning within a minute of starting injection The average rise was 34 mm systolic The diastolic pressure showed no significant change in 43 of these and there was a rise of from 8-30 mm in the others, averaging 16 mm The rise in pressure began during the injection period, reached a maximum in two to five minutes and lasted some five to twenty minutes A typical response is shown in Fig 2

The 8 subjects with "malignant" hypertension all had pressor responses, and these averaged 42/22 mm, which was rather greater than the average for the benign group

In 24 cases there was a transient initial drop in pressure, both systolic and diastolic, within two minutes of starting the injection and lasting no more than sixty seconds, being followed by a pressor response Fig 3 illustrates this response Both these responses indicate negative results

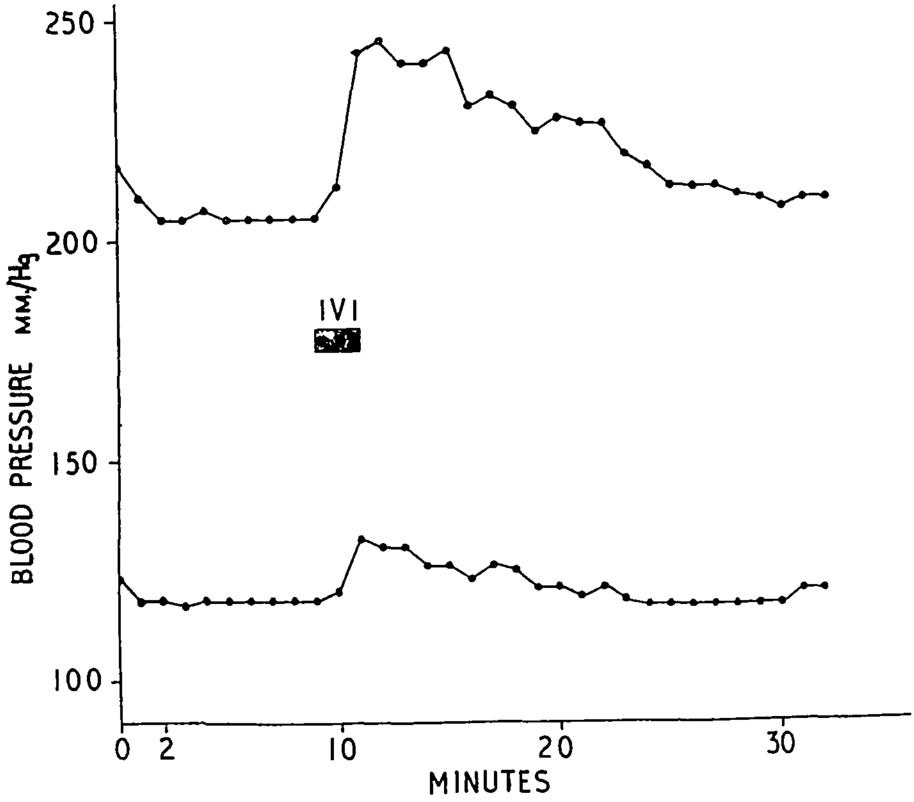

FIG 2—Patient, Mrs C A, age 62 years Benign essential hypertension F 933 test 17 5 mg I V I A typical "negative" response of blood pressure to injection of F933 in essential diastolic hypertension

In one instance (Case 127) there was a fall from 176/118 mm to 132/84 mm within a minute of commencing injection and lasting three minutes, followed by a rise to 198/122 mm (Fig 4) Repetition of the test, both in the absence of any barbiturate and one hour after administration of 3 gr of sodium luminal by intra-muscular injection, produced a similar response in each instance, the fall being from 166/114 mm to 140/92 mm followed by a rise to 212/120 mm in the former instance, and after sodium luminal from 160/118 mm to 136/90 mm followed by a rise to 200/126 mm

This patient was a woman of 61 years, with a history of headaches and dizzy turns for nine months and nocturia for "years" and with no visual upset and no tendency to sweat nor symptoms of peripheral vasomotor disturbance Her blood pressure was 206/122 mm when first seen by the house physician in the out-patient department, but was 128/84 mm two hours later in bed twenty minutes after this a reading of 180/116 was obtained although the patient was quite quiet and at rest The first test was then performed There was moderate peripheral arteriosclerosis and grade 2 retinal changes (Keith and Wagener classification, 1939) No cardiac enlargement was present and no left ventricular hypertrophy in the multiple lead E C G Radiologically there was some aortic unfolding and the cardiac area was not significantly increased Renal function was good and intravenous pyelogram normal

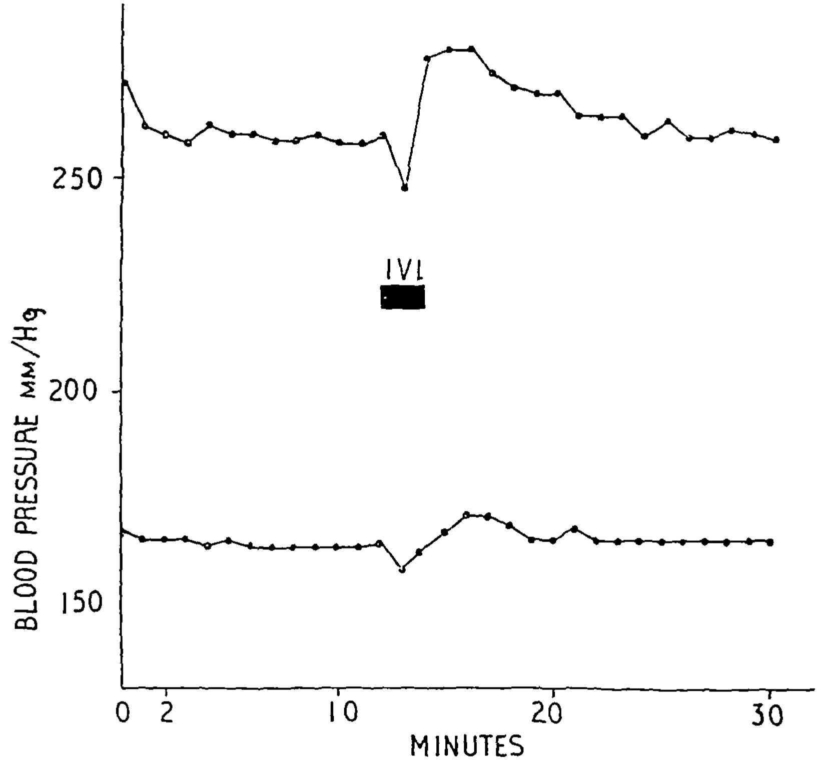

FIG 3—Patient, Mrs M G, age 32 yrs Malignant renal hypertension F 933 test 18 0 mg I V I The "biphasic" type of blood pressure response to injection of F 933

The blood pressure varied at rest from 130/86 to 214/130 following I V injection of 0 3 mg hydergine it fell from 178/110 to 142/80 during the sodium amytal test it fell from 156/100 to 122/82 Response to the cold pressor test was +28/+18

Rises in pressure were not associated with symptoms of sweating or other features and were not produced by abdominal palpation No masses were found in the abdomen

At the time the test was considered to be "negative" and the patient was discharged home She was considered unsuitable for surgical sympathectomy, and medical treatment with adrenergic-blocking drugs or the methonium compounds was not available at the time Unfortunately, this patient has so far refused to attend for follow-up examination The interpretation of this response is mentioned in the discussion

Each of the subjects presenting with a history suggesting the paroxysmal adreno-sympathetic syndrome had a clearly negative test, as did all others with labile diastolic pressures

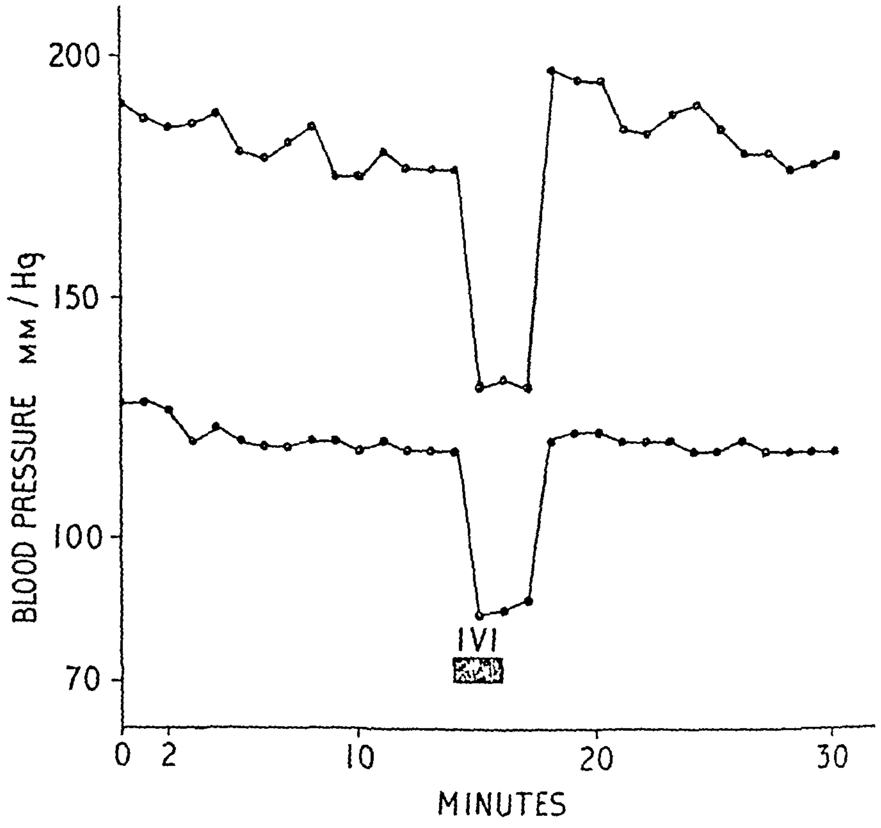

FIG 4 —Patient, Mrs R S , age 61 yrs F 993 test 16 8 mg I V I The blood pressure response in case 127 described in the text

There was no relation between the ætiological agent and the type of response in the hypertensive subjects , nor was there a statistically significant relationship between the initial resting pressure and the rise in pressure

Non-Hypertensive Subjects —Healthy normotensive subjects showed either no appreciable change in blood pressure or a mild pressor response The greatest rise in this group was 26/22 mm and the average was 12/8 mm

One of the thyrotoxics had a transient initial fall followed by a rise in pressure, and the rest responded by a mild rise averaging 17/10 mm

All the arteriosclerotic subjects had a rise in systolic pressure averaging 32 mm , and in 24 instances there was a diastolic rise as well, averaging 9 mm The 10 apprehensive subjects all showed a pressor response but not appreciably greater than the other groups, averaging 24/12 mm

2 SIDE EFFECTS —Side effects were common but, with the exception of 3 subjects, were mild and transient, lasting no more than six minutes from the end of injection Fig 5 shows the type of effects recorded in the hypertensive subjects Facial warmth, often extending to the neck and upper chest, occurred in 92 per cent and was accompanied by visible flushing of the skin in these regions in 82 per cent Sinus tachycardia was considered to result from the test when there was a rise in heart rate of more than twenty beats per minute as compared with the saline control test This was noticed in 70 per cent of subjects and accompanied by a feeling of palpitation in the chest in 13 per cent A curious sighing type of respiration occurred in 68 per cent and consisted of several deep respirations usually without any increase in respiratory rate, it was noticed towards the end of injection and lasted only for six to ten respirations Cold and numb sensations in the limbs, generally the legs, were noted by 8 per cent and a feeling of apprehension and mental tension by 6 per cent but mild headache occurred in only 2 per cent

F 933 Test

Incidence of side effects in 300 hypertensive subjects *Dose* 10 mg per square metre body surface

Subjective—	
Facial warmth	92 per cent
Palpitation	13 ,,
Cold or numb feelings in limbs	8 ,,
Apprehension	6 ,,
Headache	2 ,,
Objective—	
Flushing in face or neck	82 ,,
Tachycardia	70 ,,
Sighing respiration	68 ,,

FIG 5

In 3 subjects, all hypertensives, the side effects could be described as unpleasant and consisted of intense mental alarm and apprehension, together with the general subjective effects in a marked form lasting for up to ten minutes after injection and then gradually passing away over the next half hour Each of these subjects was among the first five to receive the test dose at a time when the investigator had little idea of the expected side effects and was inwardly apprehensive, it is possible that some of this apprehension was appreciated by the patients, although when questioned later about this none could remember if it were so or not

There was no relation between the severity of the side effects and the pressor response, nor was there a relation between the severity of side effects and the apparent placidity or anxiety of the subject before the test Reproduction of features of hypertensive encephalopathy in the 6 patients who had recently experienced them did not occur No clinical features of myocardial ischæmia were produced during or after injection in the 12 subjects with moderate angina of effort, or in the 10 subjects who had infarcts of two to eight months' duration

Only 5 subjects, including the 3 who experienced unpleasant side effects, stated they would dislike repetition of the test

In the 25 healthy individuals side effects occurred in a mild transient form in 18 subjects and not at all in the rest In the thyrotoxic group side effects occurred in all cases and were again mild and transient and similar to those experienced by the hypertensive subjects The arteriosclerotic subjects behaved in a similar fashion, and in the subjects with anxiety states side effects were no more marked than in the hypertensive group although they were experienced by all 10 patients

Response to Saline Injection—Injection of 10 ml of normal saline was carried out two days after the test in a manner exactly similar to the test dose of F 933 and subjects were not aware of a difference in the injection material There was no appreciable alteration of blood pressure in any group except the thyrotoxic subjects, in whom a pressor response of 10-20 mm systolic was obtained on the average The alterations in heart rate were not significant, and subjective effects were only noticed in 7 hypertensive and 4 thyrotoxic individuals and consisted of heavy beating in the chest in each and faint feelings in 2 of them, lasting for only a few minutes

DISCUSSION

There exists considerable evidence that the F 933 test is of value in isolating pheochromocytomas from other causes of sustained diastolic hypertension In some instances recognition of these tumours is impossible on clinical grounds alone

The technique adopted for the intravenous administration of F 933 was a simple one and was satisfactory for routine use, and it evaded the necessity of erecting an intravenous drip Particular stress is laid upon full explanation to the patient, of the purpose of the test and of what is expected of him during the test

Especial attention was paid to the frequency and severity of the side effects during and following injection In 99 per cent of the hypertensive subjects and in all the non-hypertensive subjects side effects were mild and lasted less than six minutes after the end of injection. The commonest was a sensation of warmth in the face and neck, and this was often associated with visible flushing in these areas due to peripheral vasodilatation Feelings of mental tension, sighing respirations and tachycardia are the result of the sympathomimetic action of the drug, and it is of interest in connection with the latter that production of tachycardia is one of the few adrenaline actions in the body that is not blocked by F 933

In only 3 hypertensive subjects were side effects unpleasant, and these consisted of marked apprehension and alarm on the part of the subject, together with most of the commoner effects in an intense form It is of interest that all these 3 subjects were amongst the first five to receive the test dose at a time when the investigator had little knowledge of the side effects to be expected and was inwardly apprehensive of the result of the test Some of this apprehension may have made itself known to the subjects receiving the test dose

There was no relation between the severity of the side effects and the degree of pressor response to the injection Nor was there any apparent relation between the amount of mental tension exhibited by the individual and the severity of side effects

In none of the 6 cases, who had had recent attacks of hypertensive encephalopathy, did features of encephalopathy occur during or after injection of F 933 Nevertheless, in view of the case reported by Green and Peterson, care should be taken when administering the drug to such subjects, and a suitable quick-acting barbiturate for intravenous injection should be at hand

It is probable that dibenamine would be of little use in controlling encephalopathy, since it is itself prevented from sympatholytic action, by the F 933 blockade Pentamethonium may, however, be used as suggested by Swan (1951)

It was considered unwise to employ the F 933 test in subjects in cardiac failure in view of the sympathomimetic properties of the drug , for a similar reason the drug was not administered to subjects with recent myocardial infarcts In 12 subjects with moderate angina of effort and in 10 others with myocardial infarcts of between two and eight months of age, the test dose did not produce symptoms of myocardial ischæmia

The side effects in the non-hypertensive group were never severe and were similar to those experienced by the hypertensive subjects, but less frequent

The blood pressure responses were clearly negative in all but one of the hypertensive subjects The negative pressor responses are largely the result of the increased cardiac output caused by F 933 and possibly also to a direct stimulant action of the drug on the smooth muscle of the arterioles (Nickerson, 1949) A primary adrenal medullary stimulation by F 933 is mentioned by Jourdan and Barrier (1937) but is unlikely in view of the hypotensive response in patients with pheochromocytomas In 24 instances there was an initial transient fall in blood pressure preceding the pressor response, and this is associated with the peripheral vasodilatation which occurs, especially in muscle, following injection Prunty and Swan (1950) describe these complex effects in some detail

Case 127 in whom three F 933 tests were repeated and were persistently similar, each with a significant fall in both systolic and diastolic pressures lasting three minutes, was considered negative at the time of the test Goldenberg *et al* (1950) described a subject in whom the test was clearly positive on two occasions and similar to the response of Case 127 on another occasion They consider that in such instances there is, at the time of the test, a sufficient amount of circulating adrenaline to " break through " the F 933 block Experimental work has shown that, within a certain dosage range, the greater the amount of adrenaline injected, the greater the fall in blood pressure which follows a standard dose of benzodioxane (Bovet and Simon, 1937) Further increases of adrenaline concentration require increased amounts of benzodioxane to obtain adrenergic blockade (Abdon and Hammerskjold, 1940) It is reasonable to suppose that Case 127 probably has a pheochromocytoma , unfortunately, the subject has refused all requests to return for further examination at present The lesson to be learnt is that when this unusual response occurs the test should be repeated with a larger dose of F 933

It would be wrong to attempt to draw conclusions about either the frequency of pheochromocytomas as a cause of sustained diastolic hypertension, or the reliability of the test in this series of 300 hypertensive subjects Since it is known that the F 933 test does aid detection of the tumours in hypertensive subjects it is worthwhile making use of the drug as, whatever their rarity, every effort should be made to bring pheochromocytomas to light in order that they may be removed

The purpose of this article has been to describe experience gained from practical application of the F 933 test Results indicate that the test is simple to perform and that unpleasant side effects are most infrequent By widespread application of the test it will be possible to ascertain its diagnostic usefulness more accurately and at the same time to obtain some further idea of the frequency of pheochromocytomas

In view of these facts and the apparent reliability of the test to date, the drug is to be recommended as part of the routine investigation of the hypertensive subject

SUMMARY

1 Present evidence indicates that the F 933 test is of value in aiding recognition of pheochromocytomas as a cause of sustained hypertension

2 Three hundred subjects with sustained hypertension received an intravenous test dose of 10 mg of F 933 per square metre body surface , each dose was given over a two-minute period Side effects were mild and transient in 99 per cent of subjects and were unpleasant in only 1 per cent of subjects Blood pressure responses are described, and include one unusual response probably associated with a tumour

3 One hundred normotensive individuals also received the same test dose, and in none were side effects unpleasant

4 The test is recommended as part of the routine investigation of the hypertensive subject on the grounds of apparent reliability to date

and rarity of severe side effects Certain contra-indications to the test are mentioned

I wish to express my gratitude to Dr A Rae Gilchrist for his advice and guidance and for permission to carry out the test on patients under his care, to Dr J K Slater for permission to use four patients in his charge, to Dr M Goldenberg of Columbia University, New York, for advice about the response of one subject, to Messrs May and Baker for supplies of F 933 and for checking the accuracy of samples, also my thanks are due to Mr Perrins for making up batches of the drug, and finally to Dr H R L Fraser for assisting in many tests

REFERENCES

Abdon, N O, and Hammerskjold, S O (1940), *Acta Physiol Scandinav*, **1**, 85

Barnett, A J (1950), *Lancet*, ii, 73

Binger, M W and Craig, W M (1938), *Proc Staff Meeting, Mayo Clin* **13**, 17

Bovet, D, and Simon A (1937), *Arch internat de pharmacodyn, et de therap* **55**, 15

Calkins, E, Dana, G W, Seed, J C, and Howard, J E (1950), *Journ Clin Endocrinol*, **10**, 1

Calkins, E, and Howard, J E (1951), *Journ Amer Med Assoc*, **145**, 880

Dana, G W, and Calkins, E (1949), *Bull Johns Hopkins Hosp*, **84**, 283

Drill, V A (1949), *New England Journ Med*, **241**, 777

de Vleeschhouwer, G (1935), *Arch internat de pharmacodyn et de therap*, **50**, 251

Fourneau, E, and Bovet, D (1933), *Arch internat de pharmacodyn et de therap*, **46**, 178

Goldenberg, M, Snyder, C H, and Aranow, H, Jnr (1947), *Journ Amer Med Assoc*, **135**, 971

Goldenberg, M, Faber, M, Alston, E J, and Chargoff, E C (1949), *Science*, **109**, 534

Goldenberg, M, and Aranow, H Jnr (1950), *Journ Amer Med Assoc*, **143**, 1139

Green, D N (1946), *Journ Amer Med Assoc*, **131**, 1260

Green, D N, and Peterson, E M (1950), *Journ Amer Med Assoc* **142**, 408

Grimson, K S (1950), *Surgery*, **28**, 437

Holton, P (1949), *Nature*, **163**, 217

Jourdan, F, and Barrier, R (1937), *Comp rend Soc de Biol*, **126**, 1021

Kirschbaum, J O, and Balkin, R B (1942), *Ann Surg*, **116**, 54

McCullach, E P, and Engel, W J (1942), *ibid*, **116**, 61

Mason, R E (1951), *Amer Journ Med*, **11**, 524

Morison, R S, and Lissak, K (1938), *Amer Journ Physiol*, **123**, 404

Nickerson, M (1949), *Journ Pharmacol and Exper Therap*, **95**, 27

Palmer, R S, and Castleman, B (1938), *New England Journ Med*, **219**, 793

Philips, B (1940), *Arch Path*, **30**, 916

Prunty, F T G, and Swan, H J C (1950), *Lancet*, **1**, 759

Seed, J C, and Calkins, E (1949), *Bull Johns Hopkins Hosp*, **84**, 282

Smithwick, R H (1946), quoted by Goldenberg, M *et al* (1947)

Stehle, R L, and Ellsworth, H C (1937), *Journ Pharmacol et Exper Therap*, **59**, 114

Stout, A P (1946), quoted by Goldenberg, M, *et al* (1947)

Swan, H J C (1951), *Brit Med Journ*, p 440

Taliaferro, I, Adams, R A, and Haag, H B (1949), *Journ Amer Med Assoc*, **140**, 1271

Thorn, G W, Kindle, J A, and Sandmeyer, J A (1944), *Ann Int Med*, **21**, 122

Wagener, H P, and Keith, N M (1939), *Medicine*, **18**, 317

Wilkins, R W, Greer, W E R, Culbertson, J W, Halperin, M H, Litter, J, Burnett, C H, and Smithwick, R H (1950), *Arch Intern Med*, **86**, 51

POLIOMYELITIS

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THE poliomyelitis "scene" is changing so rapidly that it is hardly possible to keep abreast of new work These rapid changes give reason for anxiety lest the victims of this disease may not obtain the full benefits of current knowledge The prevalent division of responsibility for different stages of the disease must inevitably lead to inadequacies in the study of the condition The acute stage of the disease is generally treated in a fever hospital which is often grossly understaffed, and then after three or four weeks the patient is transferred to an orthopædic centre, where the methods of treatment adopted vary between wide extremes There is need, therefore, for a critical survey of existing knowledge and of the attempts made to apply this knowledge to treatment

Poliomyelitis is dependent on the invasion of the body by a virus, which is unfortunately one of the smallest known, and is invulnerable to any of the known antibiotic drugs There are several strains of this virus, and they occur widely in both human and animal (mammalian) communities Some of these viruses live in the human alimentary canal for long periods, and during epidemics of poliomyelitis they can be recovered from sewage Carriers of the virus are likely to contaminate their hands, and thus spread infection to food Further, it has been found that house flies carry the virus during epidemic seasons In general, therefore, the spread of the virus depends on faulty hygiene

One might have thought that with improved hygiene the disease would become less common, but unfortunately the reverse seems to be the case, for the least hygienic countries have less paralytic poliomyelitis than have their modern counterparts The cause of this disconcerting state of affairs is not certain, but probably in the less hygienic countries the newly-born infant is first protected by transmitted immunity from the mother, and as direct infection is inevitable very soon after birth, immunity is built up safely during the early months of life On the other hand, infants born in the relative cleanliness of modern civilisation may live for many years without developing immunity to common strains of the virus We must therefore face the probability that a proportion of our present population of all ages have little or no immunity to poliomyelitis viruses

The current opinion regarding poliomyelitis infection is that it is primarily an alimentary canal and systemic infection which affects a substantial proportion of the population during an epidemic, but in

A Honyman Gillespie Lecture delivered on 9th April 1952 which relatively few cases of paralysis appear, and a large proportion of contacts without symptoms are found to be excreting virus in the stools

PARALYSIS AND POLIOMYELITIS

Poliomyelitis is a very minor illness in the *abortive* form, and even when meningitic symptoms develop there may be quick recovery without paralysis (*non-paralytic* form of the disease)

In the dreaded paralytic form of the disease, however, the virus exhibits some very remarkable characteristics By far the most important of these is the unfortunate affinity of the virus for motor cells in the spinal cord (motoneurones) (Fig 1) Even in the cerebral cortex this remarkable preference of the virus for the motor cell may be very obvious, as in Fig 2, where sensory and motor cortex are both seen This patient died about forty-eight hours after the onset of the major illness which developed during daily treatment with electric convulsion therapy (This was a case of Dr Kelleher's, and I am indebted to Professor A Meyer for the excellent illustrations)

Sometimes in the acute stage there has been evidence of other tissues such as muscle being invaded by the virus, but the involvement of other cells and tissues is of relatively little importance, for tissues such as muscle can regenerate For example, in Coxsackie Virus Infection, acute necrosis of muscle is followed by regeneration, and full recovery of the muscles concerned On the other hand a nerve cell once destroyed can never be replaced When there is very severe or total paralysis, over 90 per cent of the anterior horn nerve cells to the paralysed limb are found to have disappeared In other grades of paralysis also there is a close correlation between the severity of paralysis and the number of motoneurones destroyed (Bodian, 1948)

PATHWAY OF INFECTION TO NERVE CELL

There is uncertainty as regards the route of infection to the motoneurones in the spinal cord and brain It is generally thought that the virus must gain entrance to the body via the nose or alimentary tract (pharynx or bowel), but how it gets to the nerve cell is not fully known

Further, the duration of the meningitic phase before paralysis develops varies within such wide limits (from about one day to two weeks) that it seems likely that the course of events as regards paralysis remains uncertain in the early part of the meningitic stage For a time there sometimes seems to be what Sabin (1949) calls an " armed truce " between the virus and cell, and during this period the disease hovers between the allowing of complete recovery and the causing of a disastrous paralysis, in a way that is highly disconcerting to the physician

A FEW CRITICAL HOURS OR DAYS

The liability to motor cell destruction is presumably influenced by the total dose of virus and its type and by the patient's immunological state, but the curious uncertainties of the clinical course force attention on the possibility that the physiological state of the host and his cells plays an important role in deciding the fate of the motor cells For example, it is known that neither the severity of symptoms nor the cerebrospinal fluid reaction in the pre-paralytic phase bears any relation to the occurrence or not of paralysis Nor does the duration of the pre-paralytic phase bear any relation to the severity of paralysis Yet it seems probable that the fate of tens of thousands of nerve cells is decided during a period of a few hours at a critical phase of virus activity which usually seems to correspond with the early part of the meningitic stage We have no reason to think that any known treatment prevents the destruction of a single nerve cell after paralysis has become evident, and in many instances the fate of each nerve cell must have been decided before we see the patient

FACTORS WHICH INFLUENCE CELL VULNERABILITY

It is now well known that viruses enter intimately into the metabolism of the host cell, so much so that the virus particles seem to disappear at certain stages of their intracellular development Increasing attention is therefore being paid to the possibility of interfering with metabolism of the host cell At the Second International Poliomyelitis Conference in Copenhagen (1951), Dr Horsfall stated " If the objective of interrupting virus multiplication by chemical means is to be attained, present evidence supports the idea that this will come about through substances which act on intracellular components, possibly on enzyme systems, rather than on the virus *per se* "

This field of research has been opened up very greatly by the discovery by Enders (1951) that poliomyelitis viruses can be grown on cultures of human embryonic tissues Another promising field for research is provided by the study of bacteriophages (Delbrück, 1951) which act as viruses, in relation to the bacteria they infect These and other fields of research are likely to increase greatly the prospects of an effective method of treatment for the acute stage of poliomyelitis, and indeed papers are already appearing which show that certain chemical substances that interfere with certain cycles in cell metabolism also delay virus multiplication

RECOVERY OF PARALYSIS

According to Bodian's (1948) researches, the cells which are being destroyed by the virus disappear entirely in the course of a few days, as indeed may be expected from the changes seen in Fig 1 All the other anterior horn cells, though showing chromatolysis in the acute stage, recover to a perfectly normal appearance in four or five weeks' time

Within a month of the acute illness, the spinal cord looks normal again except that many motoneurones have disappeared The question then arises—why do affected muscles continue to improve in strength

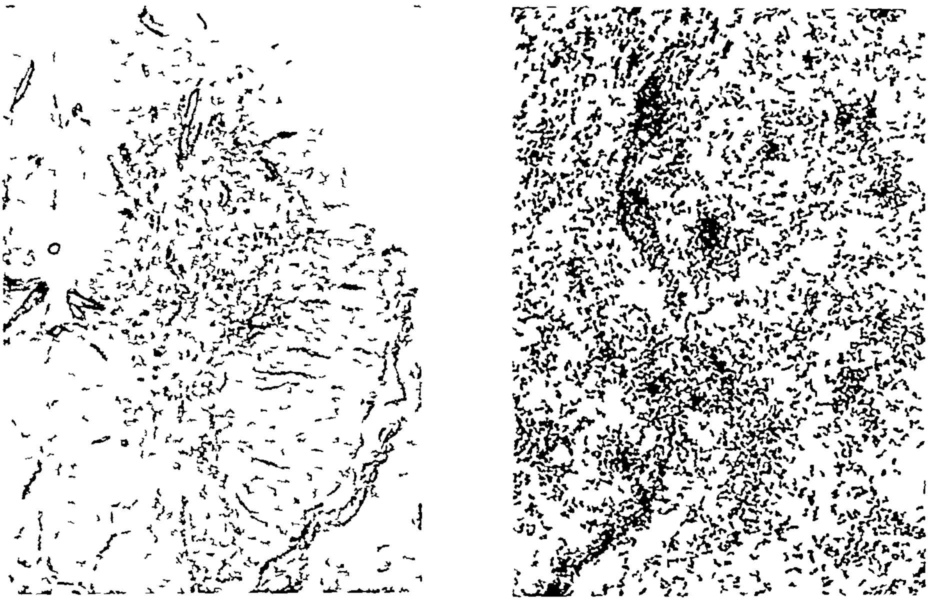

FIG 1*a* FIG 1*b*

FIGS 1*a* and *b* —Section of spinal cord from a patient who died of poliomyelitis after an illness which lasted for only a few days Nearly every anterior horn cell in the section has already been destroyed Nissl, ×12 and ×80

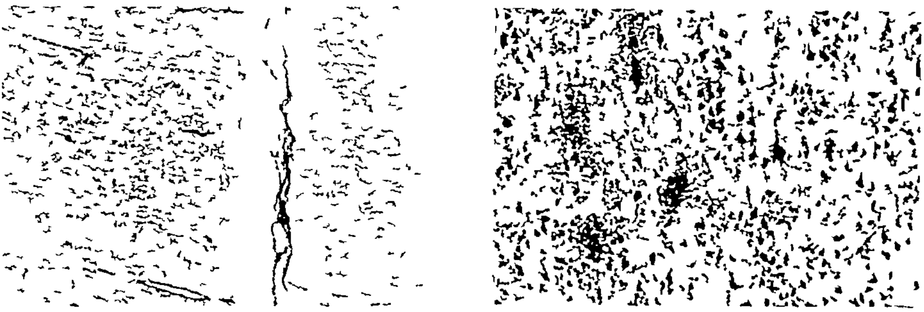

FIG 2*a* FIG 2*b*

FIG 2*a* —The motor and sensory cortex in the same case as for Fig 1 Cell destruction in the motor cortex is very evident (2*b*) while the sensory cortex seems to be intact Nissl, ×14 and ×60

for so many months or even years if the surviving spinal cord cells appear normal after a month, and are presumably fully active again within, say, two months of the acute illness? Presumably the surviving neurones which look healthy one month after the acute illness will have much the same appearance a year later and yet the recovery of motor power is much greater at twelve months than at one month As far as is known, nerve fibre regeneration does not occur in recovering poliomyelitis If the anterior horn cell is only injured to a reversible extent, Wallerian degeneration does not occur in the axon, while if the cell dies there is no possibility of regeneration There is of course no chance of nerve cells growing again, so that one can only conclude that the improved function during rehabilitation depends simply on getting the most out of the remnants of the motoneurones which survive the acute illness There are about 12,000 spinal motoneurones supplying the nerves to each limb, and in severe paralysis of that limb over two-thirds of these (8000) may have been destroyed and cannot be replaced (Bodian, 1948)

As far as is known, the gradual improvement spread over, say, eighteen months (chiefly the first nine months) is due simply to hypertrophy of non-paralysed muscle plus the gradual enlargement and improved efficiency of surviving nerve cells and nerve fibres which seems to develop under conditions of continual stress It is very obvious, however, from the wide variety of methods of treatment used at the present day, that the best methods of treating paretic muscles have not yet been scientifically established

CLINICAL EVIDENCE OF FACTORS INFLUENCING CELL VULNERABILITY

It seems desirable here to refer briefly to clinical evidence that extraneous factors affecting the patient may influence the vulnerability of his motoneurones There have, for example, been many [illegible] of poliomyelitis following local trauma (including operation) in [illegible] the paralysis developed an overwhelming preponderance in [illegible] of the body which was involved by the injury or operation [illegible] regard to tonsillectomy, it seems undoubted that poliomyelitis [illegible] ing soon after tonsillectomy tends to involve the medulla [illegible] the dangerous bulbar type of palsy

It has also become evident that poliomyelitis fol[illegible] month of a prophylactic inoculation is liable, in a small [illegible] cases, to lead to severe paralysis of the limb in[illegible] 1950) Bradford Hill and Knowelden (1950) confirmed [illegible] and further found statistical evidence which suggested [illegible] tion not only led to maximum paralysis in the [illegible] inoculation actually contributed to the development [illegible] in what would otherwise have presumably been a [illegible]

I have previously reported (1947, 1949) th[illegible] questioning a series of convalescent patients with regard to their physical activity at the onset of the disease From the figures obtained, it became evident that complete rest in bed after the onset of the major illness (meningitic stage) reduced the chances of severe paralysis to a highly significant degree, whereas there was no such correlation between the amount of physical activity taken *before* the onset of " meningitic " symptoms and the degree of paralysis The figures were so striking as to indicate that this factor seems to play a major rôle in determining whether or not severe paralysis occurs This view has been contested by several clinicians, but none, so far as I know, have studied the subject with sufficient care to justify an expression of opinion except Dr Horstmann (1950), and her figures were very similar to my own, as were her conclusions (Table) There is therefore a clear need for others to collect this kind of information so that the exact importance of this matter may be finally settled

TABLE

The Effect of Physical Activity continued after the Onset of the Major Illness, on the Development of Moderate or Severe Paralysis

	Number developing Paralysis (moderate, severe or fatal)
Dr Horstmann's cases—	
174 patients rested on first day of illness after onset of symptoms of major illness	62 (35 per cent)
173 patients did not rest on first dav after onset of symptoms	133 (77 per cent)
Dr W R Russell's cases—	
38 patients rested during the whole of 24 hours following onset of major illness	8 (21 per cent)
51 patients did not rest during the whole of the 24 hours after onset	43 (84 per cent)

OUTSTANDING CLINICAL PROBLEMS

Let us now consider a few of the problems facing the physician who has to handle a possible case of poliomyelitis The development of meningeal symptoms in any patient always raises urgent diagnostic questions, and the critical need to recognise the various forms of meningitis in their earliest stages, for treatment to be curative, greatly adds to the physician's responsibility In poliomyelitis the wide variation in the nature and severity of the meningitic symptoms may sometimes help and sometimes hinder the diagnostic problem For example, there might be either a painful stiffness of the neck or possibly an unbearable pain over the sacrum in a patient who otherwise feels perfectly well On the other hand, pains in back and muscles may be severe with fever, vomiting, retention of urine and headache In cases of spinal poliomyelitis the general mental alertness of the child is in striking contrast to the early confusion in tuberculous meningitis, but in polio-encephalitis, loss of consciousness may be an early feature There is no time here to consider further the differential diagnosis

The development of meningitic symptoms causes great alarm to all concerned, and yet it is most important in poliomyelitis that the patient should be surrounded by an atmosphere of calm and efficiency Sedation with barbiturates and analgesics should not be withheld, as restlessness and anxiety may do harm With regard to infectivity, it is likely that several members of the house and neighbourhood are already excreting virus in the stools and are just as infective as the patient As, however, less than one case in a hundred (in most outbreaks) develops paralysis, it is most improbable that more than one member of a small circle will develop a dangerous form of the illness, while the abortive cases will acquire a useful life-long immunity to the disease All questions, therefore, of rushing the patient away to protect others are unreasonable in poliomyelitis, so that the physician need consider only the patient's interests in deciding whether he should go to hospital

During epidemics the hospital beds available may be so inadequately staffed that slight cases are better nursed at home The chief reasons for transferring cases of poliomyelitis hurriedly to hospital are (1) uncertainty regarding the diagnosis, and the special need to exclude some forms of meningitis requiring immediate treatment with antibiotics, (2) rapidly spreading paralysis which is involving the muscles of respiration to such an extent that a respirator should be at hand Under epidemic conditions, therefore, circumstances may well develop under which small mobile squads would be useful to carry out lumbar punctures on doubtful cases, and maintain respiration if necessary while the patient is transferred to hospital

The development of paralysis requires a reassessment of the situation, for disasters may occur very quickly The first danger to consider is the development of difficulty in swallowing due to the bulbar type of the disease Secretions collect in the pharynx and cause a bubbling rattle with every breath In such cases the patient should at once be turned on his face and the foot of the bed raised two feet to allow secretions to drain out of the mouth and throat by gravity The patient may be transferred in this posture to hospital Mechanical aspirators (suckers) should always be available for these cases, but must be used gently Such a patient should always be " specialed " in hospital and special training should be provided for the nurses concerned Major errors in handling these cases are all too commonly observed In the first place, propping up the patient makes matters worse, while putting such a patient in a respirator is generally fatal, as the machine sucks the secretions into the lungs and causes pulmonary collapse A bulbar case should never be placed in a respirator unless the spinal muscles of respiration also become paralysed Such cases seldom survive, but steep postural drainage should be maintained in the respirator to minimise the risk of secretions or vomit being sucked into the lungs

The other major danger requiring prompt action is the spread of paralysis to involve the muscles of respiration This is recognised by a quickening rate of respiration, by loss of strength to cough, by the visible feebleness of chest and diaphragm movements, and especially by the inability to say more than one or two words with each breath (tested by asking the patient to count) When respiratory power is failing, the patient becomes restless, anxious and may even appear to be hysterical Disastrous errors in diagnosis in these circumstances are all too easy All such cases should be transferred to a hospital experienced in respirator treatment Unfortunately it cannot be said that the fever hospitals either in this or other countries are adequately staffed to handle these difficult problems, and there is anxiety in all countries as to the most suitable organisation for the early treatment of poliomyelitis The doctor may be required to maintain adequate respiration during the journey to hospital The simplest method is probably to apply intermittent positive pressure of oxygen or air to mouth and nose, and apparatus for this should soon be easily obtained in this country

With regard to the early treatment of paretic muscles, there are some wide divergences of opinion, owing largely to the unfortunate absence of accurate physiological data regarding the pattern of muscle recovery in this disease under varying circumstances , it is to be hoped that this information will be collected by research workers before long

Muscular fatigue is to be avoided at all costs at the onset of the pre-paralytic (major) illness, but gentle passive movements of joints should be carried out from the first day that paresis appears The visit by a physiotherapist once a day is inadequate for this purpose, for the joints should be moved gently every few hours It is better therefore for the nurses to receive simple instruction as to how this should be done in each case Passive movements carried out frequently in this way prevent early contractures, spasms and joint pain, and greatly reduce the need for splinting of any kind

The most usual treatment of partially paralysed muscle still involves prolonged rest in what is called the neutral position, with gentle assisted exercises This traditional method of treatment has been abandoned in many clinics, and is certainly coming under highly critical scrutiny Prolonged rest in a neutral or relaxed position may prevent or defer the development of contractures, but it also seems to delay the recovery of function in weak muscles The quickest way to strengthen a weak muscle must always be to exercise it deliberately and frequently, but how soon this should be started and how vigorously or frequently this should be done is not known, and it may vary greatly from case to case The following procedures show, I believe, how to investigate this problem , muscle groups can be safely used for experiment in any case of poliomyelitis, while untreated groups can be used as controls In the first place the partially paralysed muscles can be shown to fatigue easily and recover slowly (Fig 3), and the observation of these phen-

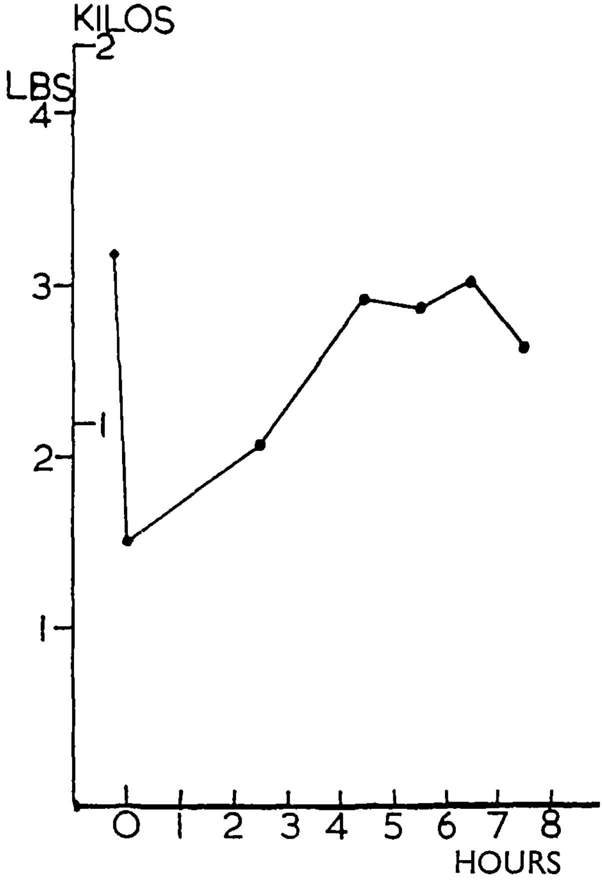

Fig 3a—Pte C *Effect of fatigue in a severely paretic triceps muscle 5 months after the acute illness* The maximum strength (measuring spring at wrist) is recorded before and after moderate fatigue At onset the patient made a maximum contraction against resistance 6 times a minute for 10 minutes, and then 12 times a minute for a further 10 minutes The resulting fall to half the initial strength and the ensuing slow recovery is shown

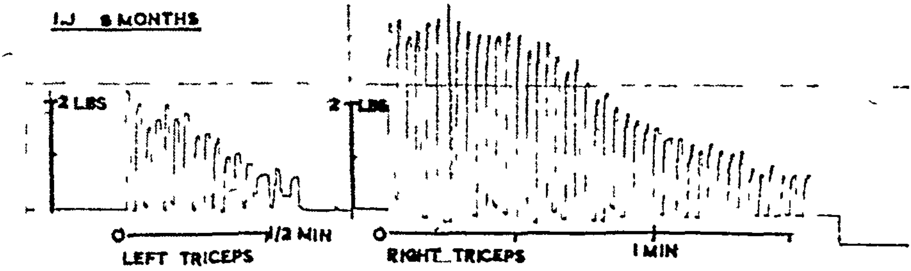

Fig 3b—Tracing on a recording dynamometer to show the rate of fatigue in the paretic muscles studied On this occasion the patient was instructed to make repeated maximum contractions at a rate which was quick but easy to operate (see time scale)

omena has frightened people and has, I believe, had an adverse effect on the scientific development of muscle re-education Further, the commonly used methods of recording muscle strength on the 0-5 code are quite unsuitable for studying poliomyelitis A simple spring balance is many times more accurate, as is seen in the following experiment a patient was instructed to exhaust his paretic right triceps muscle once every hour (as in Fig 3*b*), while the work he did was measured by a simple recording ergometer This was continued for several weeks, and after two to three weeks there was a considerable increase in muscle strength (Fig 4) Clearly this deliberately induced and repeated fatigue appeared to do good and certainly did no harm

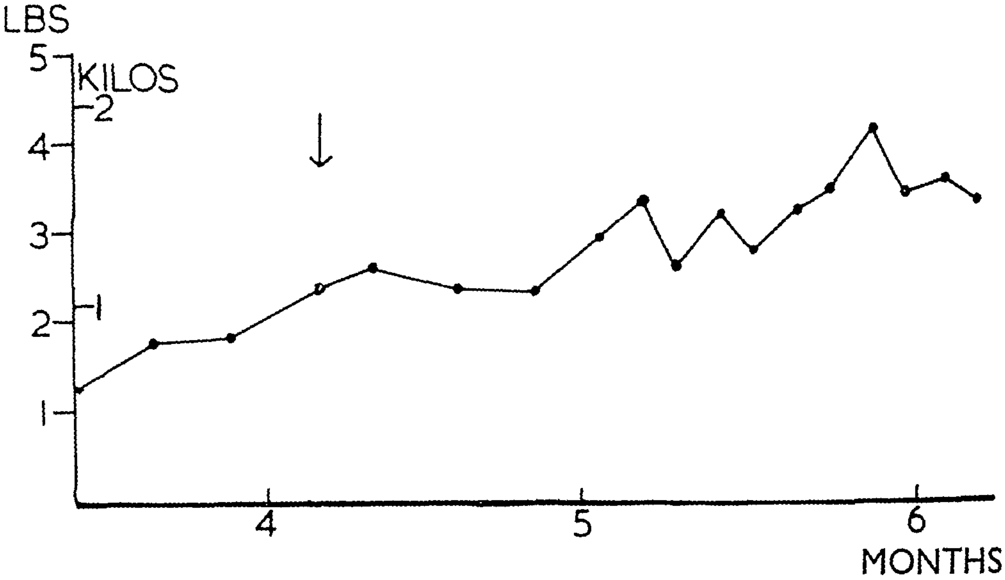

Fig 4 —Pte J *Progress in strength of severely paretic muscle (triceps) submitted to fatiguing exercises Record covers the 4th, 5th and 6th months after the acute stage* For the first 3 weeks studied no special exercises were added to ordinary physiotherapy Then (at arrow) repeated fatiguing exercises were started which were measured by a recording ergometer For 3 weeks the patient exercised once an hour for 12 hours every day, continuing repeated maximum contractions on each occasion till the muscle was fatigued to the point of paralysis This effect was produced by raising a weight of 500 g a distance of 45 cm 15 to 20 times on each occasion After 3 weeks these hourly fatiguing exercises were carried out hourly on only 4 days each week At this period the strength of the weak muscle was obviously increasing Clearly the repeated and deliberately induced fatigue had done nothing but good

There has been a curious failure to collect such simple measurements about muscle strength at different stages in poliomyelitis, and the result is that we do not yet know the optimum plan for retraining weak muscles There should, however, be no great difficulty in correcting this unfortunate state of affairs After studying the theoretical aspects of the problem, and the recent American experience of robust methods of rehabilitation in polio, it seems to me very probable that within the next few years we shall see great changes in our methods of handling the stages of recovery in this country, and that these changes may well halve the average time spent in hospital by cases of paralytic poliomyelitis

It seems necessary, however, to have a few special centres where the disease can be followed from start to finish by people experienced in studying the physiology of both muscle and nerve

Units of this type are required to determine beyond all argument what are the optimum methods of handling the acute stage of the disease, and its dangerous complications such as bulbar paralysis and respirator paralysis

They must attempt to establish the best treatment for paretic muscles at all stages of the acute and the recovery phases They must learn to determine as soon as possible what degree of recovery is to be expected, to plan the patient's life accordingly, and to learn how soon under varying conditions it can say to the patient "to stay in hospital longer is a waste of your time"

Knowledge of the disease is progressing so rapidly that special centres are required also to study the clinical application of research on nerve cell metabolism to a degree sufficient to enable the patient to benefit from what is discovered without undue delay

Such a unit should act as instructor to other centres, and would set up a model for others to copy It would be gratifying if Scotland were to play a leading rôle in this development

These thoughts may not seem of much importance with the incidence of poliomyelitis standing at the present low figure, but if we are likely to experience major epidemics of the disease in the future, then the more preparation we can make, the better

I am specially indebted to Dr E H J Schuster, O B E, D SC, for constructing apparatus used, and to Dr J M K Spalding for making the muscle records

REFERENCES

BODIAN, D (1948), in *Poliomyelitis* (1949), (Lippincott Co)

BRADFORD HILL A, KNOWELDEN, J (1950), *Brit Med Journ*, 2, 1

DELBRUCK, M (1951), *Second International Poliomyelitis Conference* (in the press)

ENDERS, J F (1951), *Second International Poliomyelitis Conference* (in the press)

HORSFALL, F L (1951), *Second International Poliomyelitis Conference* (in the press)

HORSTMANN, D (1950), *Journ Amer Med Assoc*, 142, 236

McCLOSKEY, B P (1950), *Lancet*, 1, 659

RUSSELL, W R (1947) *Brit Med Journ*, 2, 1023

RUSSELL, W R (1949), *Brit Med Journ*, 1, 465

SABIN, A E (1949) *Ann Int Med* 30 40

THE CASE FOR WIDE RESECTION IN CANCER SURGERY

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IT seems to me that within recent years there has been manifest in surgical practice an increasing boldness in attempts to eradicate malignant disease We can account for this more aggressive trend in a variety of ways

First, and probably most important of all, there have become available to the surgeon, several new and immensely powerful ancillaries, such as the antibiotics, blood transfusion, better anæsthesia and the like With their help even the average surgeon can now tackle with relative safety and with reasonable assurance, major resections, which formed earlier the rare and critical accomplishment of only the master technician It would be surprising then, if in reply to cancer's ever-present challenge, surgeons did not re-engage in battle, this time with new weapons and with new tactics, a doughty opponent who has all too often clearly been the victor in earlier conflicts

Second, the careful follow-up of patients and its complete analysis, has made him acutely aware of the inadequacy of our management of cancer at many sites, and has encouraged him to try to effect some improvement There has been, for example, a keen realisation that, whereas an increasingly large proportion of patients with cancer at various sites have been surrendered almost entirely into the care of the radiotherapist, palliation rather than cure, is often the admitted objective It is not unnatural that, especially where these results have been little better than bad, a new generation should want to try again where its predecessor has failed

Thirdly, the surgeon has come to rely increasingly for guidance on the pathologist, who by a careful analysis of biopsy and operation specimens and of autopsy material, has made clear the inadequacy of many of our accepted operative procedures He has also provided the surgeon with a wider and more complete knowledge of the expected behaviour of tumours at all sites, which is of immense value in planning management and in hazarding a prognosis

It is on some aspects of this widening surgical assault on the cancer problem that I propose to comment It seems to me that this attack has developed in a variety of different ways, which I now propose to review in turn It will soon be evident that my separation of these various lines of development is somewhat artificial, just as it will be

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A Honyman Gillespie Lecture delivered 17th April 1952 obvious that I have given a very free intrepretation to what constitutes a "wide resection" in cancer surgery When considered together, however, they can be taken to represent what we may call

THE CASE FOR WIDE RESECTION

(1) *By electing to carry out at an earlier stage a wide operation for the removal of a tumour which the force of events is likely to compel us to do later on, even in the knowledge that, by doing so, we may be asking the patient to accept considerable deformity and disability*

A basal cell skin cancer is, in general, one of the least noxious forms of malignant disease Failure to eradicate it at the outset, however, whether by radiation or by surgery, seems often to be the prelude to a life-long losing battle against relentless extension of the tumour It is probably true that the incident of failure corresponds in time to the spread of the tumour to mucous membrane, to cartilage or to bone Here it seems to establish itself with a persistent penetration that is always just ahead and just beyond repeated nibbling efforts at surgical extirpation Of the mutilation which may result we are well aware

I am satisfied that there comes a time in the management of such a patient when we should tackle the problem with complete ruthlessness Timid and limited procedures cautiously practised in the hope that something less than "radical" may be adequate, are doomed to failure We must, of necessity, do forthwith what the force of circumstance is likely to make us do later on and then with little expectation of cure

(2) *By the selection earlier in the disease of an operation normally reserved for the more advanced case*

We can none of us be complacent about our present efforts to cure malignant disease in the stomach It is true that the average man's natural reluctance and the insidious character of gastric cancer, contrive together to bring very many patients to us too late for cure But when we consider the relatively few favourable patients who survive gastric resection, undertaken in the hope of cure, we are very lucky if we salvage one in five Nor has any alternative method of treatment presented itself which holds out any reasonable prospect of improving such a depressing state of affairs Little wonder then, that the case is now being argued for the acceptance of total gastrectomy as the standard operation in the treatment of cancer of the stomach, omitting only growths at the cardia, which constitute a somewhat different problem

First let us enquire what are the limitations of an adequately performed subtotal gastrectomy in the treatment of cancer of the stomach

The incident of blood spread (57 per cent incidence of microscopic vein involvement Meissner, 1949) or of transcœlomic transfer, probably determines, at the very onset, either death or survival, so we must content ourselves with attempts to resect the local extensions of the tumour along with the regional lymph drainage area Now, if it is true that, of patients dying from cancer of the stomach, the tumour is found at autopsy to be confined to the stomach in anything from 10 to 20 per cent (Warren, 1933 , Abrams, Spiro and Goldstein, 1950) then our efforts should not be in vain

Most of us would like to believe that we can usually keep well clear of the edge of the tumour in the stomach (always provided it is not embarrassingly large), and local recurrence in the gastric remnant does not feature large in our recollection of the disposition of post-operative recurrence Nor are we now misled by the myth of the inviolable duodenal barrier to extension of cancer in that direction Microscopic spread well beyond the grossly apparent outer limit of the tumour, especially in the submucous coat is, however, a feature of gastric cancer, and an error as high as one in four in estimating at operation the upper margin of the growth has been reported (Coller, Kay and McIntyre, 1941 , see also Meissner, 1949 , Scott and Longmire, 1949) It is true that the microscopic extension is seldom more than 4 cm beyond the edge of the tumour, as estimated naked eye at operation (Verbruggen 1931), but then 4 cm is quite a long way when resecting high up on the lesser curve There should, therefore, be little surprise at the high incidence of local recurrence reported in the literature in recent years (Lefevre, 1947 , Warren quoted by Lahey and Marshall, 1950 , McNeer, Vandenberg, Donn and Bowden, 1951 , Berne and Freedman, 1951, but *cf* Thomas, Waugh and Dockerty, 1951 , Harvey, Titherington, Stout and Fordyce, 1951) This evidence certainly suggests, that when we carry out what we honestly believe to be an adequate subtotal resection for cancer, we fail to get beyond the local extension of the tumour, very often in the case of its upper margin and, not uncommonly too, in relation to its lower limit as well

Our failure in relation to lymphatic spread is probably even more significant, when we remember that the percentage of incidence of node involvement has been computed to be as high as 88 per cent (Coller *et al* , 1941) and that, even in the absence of positive nodes, there may still be widespread infiltration of lymphatic channels in and around the stomach (Meissner, 1949) Deposits may also be encountered, not only in the obvious lymph nodes in the greater and lesser omentum but, often rather unexpectedly, at the hilum of the spleen (21 per cent , Eker, 1951), or in relation to the tail of the pancreas Little wonder then, that in a high percentage of cases following subtotal resection the tumour first recurs in lymph nodes in the immediate vicinity of the stomach (McNeer, Vandenberg, Donn and Bowden, 1951) If it can be proved that these nodes can be more adequately removed by carrying out a total resection, then this must surely be a very strong argument in favour of the more radical procedure And such indeed is the inference that one can reasonably draw from recent work (Eker, 1951) where a searching examination of cleared operation specimens following total and subtotal resection, revealed in the first a significantly greater number of lymph nodes than in the second It is, however, argued just as convincingly from the Mayo Clinic (Thomas *et al*, 1951) that by a carefully executed radical subtotal resection it is possible, and with more safety, to remove the regional lymph nodes just as widely, as by a total resection, with the exception of a small group of nodes tucked in around the cardia

In any event, even if we admit that total resection holds out some promise of achieving a more complete local excision, and that it may even render possible a more nearly adequate removal of the area of regional lymph node metastases, can we honestly sanction it as a routine operation for gastric cancer ?

Firstly, are we satisfied that, from the pathological point of view, it is a really satisfactory " en bloc " operation ? I believe the answer to be " no " It fails (1) at the cœliac axis where division of the vessel is not feasible proximal to the point of origin of the left gastric artery, (2) where one must spare the hepatic artery in the right free margin of the lesser omentum, and (3) the most significant of all (and here the total operation can be no more effective than is a subtotal resection) in the inaccessible area in relation to the gastroduodenal artery and to the head of the pancreas Little wonder then that one team of total gastrectomy enthusiasts (McNeer, Sunderland, McInnes, Vandenberg and Lawrence, 1951) is striving to extend the limits of the operation to include the body as well as the tail of the pancreas and the spleen, and the retro-peritoneal tissue below the diaphragm, this last approached through a plane of cleavage which lies behind the vascular arches of the foregut loop—a dissection which had earlier been suggested *(Allison and Borrie, 1949) in relation to the more complete removal of* tumours at the cardia But even when the limits of resection are pushed thus far it still remains, from the pathological point of view, an incomplete and somewhat unsatisfactory operation

Secondly, although in the best hands, the operation whether completed from the abdomen or from the chest or by a thoraco-abdominal approach, can be accompanied by a mortality that compares not unfavourably with that which follows a partial resection (9 5 per cent , Scott and Longmire, 1949 , 5 3 per cent Walter, Gray, Priestley and Waugh, 1950 , 9 4 per cent Lahey and Marshall, 1950) Can we more ordinary people reasonably expect to reproduce such good figures, or will not a prohibitive mortality and a high morbidity more than outweight the few successes which may follow the wider resection ?

Thirdly, is life after a total resection compatible with comfortable survival ? On this issue there is widely conflicting evidence, and, in its evaluation, I have no personal experience to guide me It is clear that a diminished capacity to take food in any great amount, and distressing symptoms of " dumping," go hand in hand with failure to gain weight—

an old man in poor circumstances can come near to death from starvation Add to that the risks of dysphagia, diarrhœa, vitamin deficiency and anæmia, and it is apparent that, although there is a minority who can apparently return to full productive capacity in a tolerably good state of health (Farris, Ransom and Coller, 1943 , Smith, 1947), life for the remainder often continues to be one of sem-invalidism (Stammers and Brain, 1951)

Fourthly, does the more extensive operation offer a better chance of cure ? This question is as yet unanswered It is still the standard practice, in this country at least, to reserve the total operation for the worst cases, with a massive tumour, for the removal of which a subtotal resection would obviously be inadequate, or for the uncommon linitis plastica (Pack, McNeer and Booher, 1947) The results following its use under such circumstances are bound to be bad However, active canvassing (and, surprisingly enough, by even such a cautious campaigner as Lahey (Lahey, 1950) has, in the American continent converted a not inconsiderable body of surgical opinion to advocating total resection as the standard procedure for even the early case—what has been called (Lefèvre and Lortat-Jacob, 1950) " la gastrectomie totale de principe " in contrast to " la gastrectomie totale de nécessité " —the standard total resection of our experience from which, alone, we tend to judge the merits of this operation Now the success of the Miles operation for rectal cancer (and its less important limitations too) lies in its completeness for a lesion at any site, and in his insistence on its practice for the smallest and most favourable tumour It may well be that total gastrectomy may similarly come to earn a dividend, when it is applied routinely, as the operation of choice for every gastric cancer, however small It is, however, right, I believe, that there should be some reluctance to exchange the relative safety of suturing even a tiny gastric remnant with a firm peritoneal coat, for the uncertainty of an œsophago-jejunal anastomosis (Thomas *et al* , 1951) Perhaps we should be intent rather on extending the scope of the operation only in the direction in which the site of the tumour suggests that spread would be most likely (Harvey *et al* , 1951) Unfortunately, here again the evidence of pathology affords us no encouragement since several workers have found little correspondence between the site of the primary and the direction of the main line of lymph node involvement (Coller *et al* , 1941 , Meissner, 1949 , Eker, 1951)

It may well be, that in the coming years we shall have news of encouraging improvement in the results following total gastrectomy, but, so far as I am aware, there has been as yet no published reports of an extended trial of total gastrectomy as the operation of election in all resectable stomach cancers We should, I feel sure, make trials of this operation, but I am all for embarking on such efforts with a healthy scepticism, and I am not encouraged to expect any real improvement in the outlook of a patient with cancer of the stomach as the result of such an enterprise

(3) *By extension of the principle of the "en bloc" operation*

The ideal cancer operation at any site is the "en bloc" resection of the primary along with the adjoining tissue up to and including the regional lymph nodes In the colon and rectum, for example, this has been established as the standard practice, and within recent times there have been many attempts to devise similar operations at other sites

One interesting development of this type has been the elaboration of operative techniques to allow of a comparable resection of the more accessible mouth cancers Most of this work has been carried out in the United States, and several papers have appeared in recent years describing a variety of surgical procedures of this type (Sugarbaker and Gilford, 1946, Slaughter, Roeser and Smejkal, 1949, Edgerton, 1951, Ward and Robben, 1951, Kremen, 1951, Carroll, 1952) An increasing dissatisfaction with the results of radiation therapy has largely stimulated this interest, and, even in clinics where surgical methods have been regarded with some favour, the practice of treating the primary and the cervical lymphatic network, as quite distinct and separate problems, has never seemed to be in accord with the evidence of pathology There has also been a not unreasonable feeling that, bearing in mind the infrequent but still quite remarkable success achieved years ago by men like Butlin and Trotter, it is high time for us to re-evaluate the results of surgery in this field Having seen something of this type of work in the Memorial Hospital in New York, I am satisfied that such methods of surgical treatment are well worth a trial It is true that an excision which involves dissection of the neck nodes is a formidable one, but the mortality of such procedures, even in the old poor-risk subject, is much less than that which follows an abdominal operation of corresponding magnitude Usually it is necessary to resect the intervening jaw to improve access and to facilitate closure But even in these patients the morbidity is astonishingly low, always provided an adequate airway is maintained in the early post-operative period by tracheostomy, a good nutrition is assured by generous diet given through an œsophageal tube and fistula formation prevented by a meticulous multi-layer closure Lesions of the tongue, floor of mouth, alveolus, lip, and even the anterior pillar can be dealt with in this way, and precisely the same principles are applicable at other sites in the neck, as, for example, in removal of a malignant tumour of the parotid, larynx or thyroid, always in continuity with a neck dissection Nor is the functional disability which follows other than acceptable in the vast majority of cases, early troubles with mastication can be overcome with the help of a high protein sloppy diet, and articulation is as a rule only slightly impaired In the successful cases no doubt plastic reconstruction can be entertained, but I would counsel due caution before embarking on any ambitious repair

With some slight hesitation I would like at this point to say something of malignant melanoma, in some ways the most tragic of all malignant tumours, occurring, as it does so often, in the young and healthy, with such sinister and fatal development, from such trivial and insignificant beginnings Although the " en bloc " operation first suggested by Hogarth Pringle (1908) goes some way towards satisfying the requirements of observed pathological behaviour, only too often there is the disappointment of local recurrence or of metastases, somewhere between the primary lesion and the proximally situated nodes For such a highly lethal disease might there not be the strongest argument in favour of the most radical and mutilating surgery, for even a fore- or hind-quarter amputation, for lesions on the extremities (Pack and Ehrlich, 1946, Bowers, 1949, Pack, 1951)? We turn from such a suggestion with abhorrence, certainly as a primary operation Firstly, because it seems so unreasonable to remove so much, for what may be a minute primary lesion, secondly, because we cannot be certain that by even such a devastating operation we are going to improve materially the prospect of survival, and thirdly, because we fear that a less radical operation might by chance achieve a cure But it may be, that we should turn to any measure which holds out any promise of bettering the present five-year survival rate of 28 per cent (Wright, 1949) The same argument might be used in relation to malignant synovioma, which has a predilection unusual among mesodermal tumours, to metastasise by the lymph stream It is true that such few reports as are available about fore- and hind-quarter amputation for these two very grave forms of cancer are very far from being encouraging, but then they have been tried in almost every instance only as a last resort

(4) *By a wider resection where we have pathological evidence which suggests that only by so doing can we make the operation complete*

There has been evident dissatisfaction within recent years with the standard operation for the resection for left colon cancer A high proportion of C2 (Dukes) cases and, in general, poorer results than follow right hemicolectomy (although this is not evident in every series, *e g* Welch and Giddings, 1951) have led to efforts to render more complete the resection of the lymph node-bearing area Such attempts necessarily involve more proximal ligation of the main arteries For example, in the case of a tumour on the summit of the sigmoid loop, division of the inferior mesenteric at its point of origin renders obligatory an anastomosis well below the level of the peritoneal reflection, at a point where the viability of the rectal stump is dependent on blood supplied by the middle and inferior rectal vessels (Welch *et al*, 1951, Deddish, 1950 (*b*), Gilchrist, 1950) A complete operation for the resection of the extra-peritoneal rectum would similarly make necessary a mobilisation of the splenic flexure to allow its delivery in the lower abdomen as a terminal colostomy It is true that a resection of this type is somewhat more formidable than is our usually more restricted removal Even if we are unwilling to accept this as our standard procedure, however, there would certainly seem to be every justification for such an operation when there is evidence of involvement of the lymph nodes at or above the customary point of vascular ligation In support of a wide resection of the mesocolon, there is the additional argument that spread along the gut to adjoining paracolic nodes has been noted to occur in a very high proportion of cases, where there is a diffuse infiltration of the more proximally situated lymphatics (Grinnell, 1950)

Energetic attempts are now being made to extend the limit of the abdomino-perineal resection to include the para-aortic chain of nodes, on one or on both sides, as well as to make a complete clearance of the node-bearing tissue in relation to the main vessels of the pelvis and to the adjoining viscera (Deddish, 1950 (*a*)) A 16 per cent involvement of nodes not normally included in the routine Miles resection has been reported, a figure which rose to 24 per cent when only advanced cases were considered (Deddish, 1951)

Some recent work in relation to the significance of adhesions discovered at operation for the resection of colon and rectal cancer has also some bearing on the extent of the excision necessary to achieve cure When we are confronted by a cancer of colon which is attached across the peritoneum to an adjoining viscus, we are often tempted to regard it, too hopefully, as due probably to an inflammatory cause, and acting on this assumption to separate the two by blunt dissection It seems that adhesions of this type are seldom due entirely to inflammatory causes , it is always wise to assume that under such circumstances the cancer has already penetrated at least as far as the serous coat (Sugarbaker, 1946 , Sugarbaker and Wiley, 1950)

(5) *By pushing to the limit the extent of surgical excision where we have every reason to hope that there is only wide local infiltration without distant spread*

Surgery of this sort is bound to have many disappointments but even the most heroic procedures are justified at certain sites Chief among them is cancer in the colon, and we must all number in our experience happy survivals after extensive operations which have involved removal of segments of adjacent bowel, abdominal wall, bladder, liver and the like These are the tumours which, proudly mounted in bottles, largly go to furnish impressive trophies in our surgical pathology museums Even in the presence of widely infiltrating local extension of the disease there may still be minimal lymph node involvement (Sugarbaker and Wiley, 1950), and we must never be dismayed either by the size of the primary, or by the magnitude of the dissection required for its removal

Following the lead of Brunschwig (1948, 1949) wide resections are now being employed in attempts to eradicate infiltrating pelvic tumours, whether primarily in the female genitals or in the bladder or rectum The technical problems involved are, however, much more formidable than is commonly the case with colon and rectal growths, and the difficulties of safely diverting the urinary stream cannot yet be said to have been satisfactorily resolved (Bricker, 1950)

Similar wide local removal is justified for the well-differentiated accessible cancers of the mouth which may be astonishingly late in metastasising to regional nodes

(6) *By a planned attack on recurrent disease*

Wangensteen (1949, 1950) has in recent years become the exponent of what he calls the " second look " a conception of extended cancer surgery which, so far as I am aware, is primarily his own Experience led him to believe that there is often, in the natural development of recurrent cancer, a long and insidious period of latent growth before it becomes clinically obvious He has further been impressed by the ease with which persisting or recurring cancer can often be removed surgically These two beliefs have encouraged him, in the case of cancer of the colon, where at the primary resection there was histological evidence of regional lymph node involvement, to counsel a " second look " four to six months later This is an exploratory laparatomy carried out in spite of a complete lack of symptoms If cancer is still present and lends itself to excision, a second or even a third or fourth " second " look becomes obligatory at intervals of six months, maybe each time in the complete absence of any symptoms, until a negative exploration suggests that further searching is no longer necessary Any reluctance on the part of the patient to submit to further exploration is apparently overcome by a frank statement of the threat to life from possible persisting cancer He has as yet published little on the results of such a compaign, and the story of his first case impresses one more by the undoubted courage of his long-suffering patient than by the wisdom of the method itself For my own part, I am not satisfied that one knows enough about the natural history of persisting cancer in the abdomen untreated, to assess the real value of this plan of treatment In any event, I would find it difficult, in the complete absence of all symptoms, to press with any firm conviction for a further laparatomy

(7) *By an obstinate refusal to admit defeat when confronted by a recurrence*

I think it may well be that if Wangensteen has so far failed to convert many surgeons to the philosophy of the second look, his enthusiasm has encouraged not a few to be more venturesome in the management of suspected or of overt recurrence

There must be many cases now on record where the disappointment of discovering a local recurrence at the site of anastomosis following an anterior resection for a rectal cancer has not deterred the surgeon from carrying out later an abdomino-perineal resection with every expectation of ultimate cure (Goligher, Dukes, Bussey, 1950)

It was Alexander and Haight (1947) who first made it clear that, under certain conditions, a reasonable case can be stated for the resection either by lobectomy or by the segmental method of a secondary deposit in the lung For example, the primary must be controlled and the secondary be, not only solitary, but strictly confined to the lung parenchyma The histology of the tumour is obviously highly significant in guiding the selection of the suitable case and of the relatively small number dealt with in this way to date (Seiler, Clagett and McDonald, 1950), colonic adenocarcinoma has been the commonest tumour with hypernephroma and fibrosarcoma as less frequent alternatives In general, the longer the interval between the resection of the primary and the first appearance of the secondary, the more one should be encouraged to go ahead in the belief that the slowness of development in the recurrence points to a high natural resistance on the part of the host (Dunphy, 1950)

(8) *By a refusal to regard with abhorrence any surgical excision however devastating which is conceived and executed with the sole object of achieving cure*

I would regard this as a somewhat dangerous philosophy more in keeping with what one has heard of surgical method in Germany in bye-gone days than with the more cautious approach so characteristic of our own race On the other hand, one must admit that our native squeamishness is not always in the best interest of our patients, and I should never exchange an extensive operation, for any less satisfactory method of treatment, just because it seems an easier way out The sentiments which have encouraged the dangerous practice of anterior resection, to avoid colostomy, are engendered by somewhat similar considerations

(9) *By extending the scope of the operation for cure where the results of present treatment have proved to be disappointing*

Each year carcinoma of the breast claims in England and Wales alone just over 7000 victims of whom roughly one in five is under the age of forty-five This is a disturbing record for it is not a new and unfamiliar disease, and is, at the outset, almost a superficial tumour as readily accessible to the surgeon's knife as to the patient's palpating hand We blame patients for coming too late, when the disease is already too far advanced, but we fail at the same time to campaign vigorously for earlier diagnosis And we do worse than that, or so, at least it seems to me As I recollect, the management of breast cancer was no problem when I was a house surgeon in the Royal Infirmary fifteen years ago Operation " when feasible " was the rule, and the criterion of " feasibility " depended largely on the enterprise or lack of it in the surgeon, or alternatively on his good judgment or the reverse, which is a more charitable and probably a more accurate way of expressing it Time may well prove that the " Edinburgh method " of treatment so widely held with so little regard, is nearer the solution that is present orthodox practice, but be that as it may, its introduction by McWhirter (1948) has had, I believe, the infinite merit of disturbing, in some degree, the shocking complacency with which most surgeons regard the present management of breast cancer For even in the favourable group —the clinical Stage I—when there are no detectable axillary metastases, even the best salvage rate is 80 per cent It is true that often the patient's fate has already been determined by the accident of venous spread, in the face of which, even the most radical resection is so inadequate It is also true that, when in the review of Stage I operation material, a pathologist, even the most conscientious, reports freedom of axillary node involvement, the painstaking cutting of serial sections may unmask a diagnostic error as high as 33⅓ per cent (Saphir and Amromin, 1948)

And, in any event, have we any right to call the standard operation a " radical " mastectomy As we shave off the breast and pectorals from the chest wall, do we wilfully forget the internal mammary nodes, separated from our knife by only a few centimetres, and situated in turn on a short cut to the root of the neck and in the closest proximity to the parietal pleura ? It is true that cancers are commonly in the lateral half of the breast and that local recurrence in the anterior mediastinum does not often confront us in clinical practice But when we talk of the " radical " operation can we honestly overlook the work of Handley and Thackray (1949) for the implication of their findings is immensely significant and it has been abundantly confirmed in the recent contribution of Dahl-Iverson (1951)

If the limit of the resection in depth must be regarded as highly unsatisfactory, nothing better can be said of the upper and lateral limit of lymph node removal, somewhere in the inaccessible corner between the clavicle and the first rib—a significantly long way short, of the point, where the lymph drainage system eludes our further pursuit, by emptying into venous channels For it was in this area that Andreassen (1947) found a 21 per cent recurrence rate after the radical operation, and when later (Dahl-Iverson and Andreassen, 1949) he undertook routine supraclavicular node dissection (when there was clinically no suspicion of their involvement) he found them to contain deposits of cancer cells in one out of every three cases with positive axillary nodes Should we then extend the operation in all cases where there is already axillary node involvement to include a resection of the supraclavicular nodes ? It was Halstead's practice (1907) to do a complete dissection from the clavicle to the carotid bifurcation whenever he encountered at operation metastases at the apex or even at mid-axillary level Although this meant extending the operation in rather more than half his cases, it was completed with a low operative mortality Unfortunately, the salvage rate was little encouragement to such enterprise Haagensen and Stout (1943) have now relegated to the " categorically inoperable " all patients with clinical evidence of supraclavicular node involvement, yet they continue to sanction the " radical " operation when there is cancer in the axilla, although we are told that in one-third of these, the nodes above the clavicle are, at least microscopically, already involved Does not all this add up to the frightening inadequacy of the " radical " operation, and little wonder that Lees and Park (1951) have attributed such improvement as follows surgery to no more than the wise selection of the patients in whom the disease seems likely to run a more benign course Are we then to abandon surgery as our primary method of treatment, or will we be undismayed and accept the challenge as Wangensteen (1950) (in discussion, Taylor and Wallace, 1950) has done and pursue the disease beyond the clavicle and into the mediastinum, splitting the sternum to clear the lymphatics from around the great vessels and the internal mammary chain ? I do not pretend to know the answer, and I would be reluctant to defend the practice of such wide resections, but of the depressing results at present achieved in breast cancer I am acutely aware as I am conscious of the limitations of the " radical " operation in even its local resection

(10) *By an elaboration of new techniques which allow of resection of cancer at sites previously considered inoperable*

It is only within the last decade that attempts at surgical cure of cancer of the œsophagus have become at all frequent When the risks of exploration across the pleural space has been removed, and the possibilities of restoration of continuity had been established, not by the tedious fashioning of an ante-thoracic œsophagus, but by anastomosis of the stomach even high up in the mediastinum, there was every hope that surgical endeavour might, at long last, hold out some promise of cure in this very lethal cancer Unhappily there has been as yet little encouragement or reward in this field of surgery, where a low resectability rate, a high post-operative mortality and a small per cent of ultimate cures seem still to be the rule Similarly, the enthusiasm which greeted Whipple's early efforts (1938) to resect malignant disease in the pancreas has now largely abated and the operation, at least for lesions in the head and body, likely to be practised with a declining frequency (Cattell and Warren, 1951 , Loggan and Kleinsasser, 1951) The results of resection of ampullary tumours are, however, highly gratifying, always provided the diagnosis can be established at an early stage, and here at least a new technique has brought the occasional success

The lead given in this country by Gordon-Taylor (1935) has been largely responsible for the increasing recourse to the hind-quarter amputation He was able to record early this year (1952) no less than 50 cases from the practice of the Middlesex Hospital alone For the cure of the massive secondary chondrosarcoma of the innominate bone or of the upper end of the femur, experience seems to justify it unquestionably, although in the management of the more lethal of the primary bone tumours the results are not so encouraging (Coley, Higinbotham and Romieu, 1951)

The Case for the other Side

I believe that all the many arguments which have been adduced at one time or another, in support of a widening of the surgical treatment of cancer, deserve our closest attention At the same time, it is increasingly apparent that we must continuously and critically examine the implications and results of this trend in our surgical approach For even in these types of cancer for which wider surgery is pled with most earnestness, a strong case can equally be made, if not for conservatism, certainly for the exercise of reasonable restraint I have already touched on many of the points which may be argued in making the case for the other side, but perhaps I might now be allowed to marshall a few of them together

(1) By extending our surgical excision, we may be inviting a prohibitive mortality Are we right to sacrifice more, in the hope of curing more ? Is it reasonable to deny a short span of life, maybe months, maybe years, to many in the hope of extending life usefully to a few ? Are the extra lives we lose in the immediate post-operative period, made good by the prolonged survival of a small number or by the ultimate survival of a handful ?

(2) All too often, extensive operative procedures are followed by a distressing morbidity Are we going to add to the burden of the cancer sufferer the trials of a long and complicated post-operative period with no certain promise of cure in the end—the intractable fistula, the sloughing and slow healing of skin flaps, the large infected cavity and its painful healing

Mixed up inextricably with this aspect of the problem is the difficult question of palliation, and bound up in it too is the surgeon's reluctance to define terms such as " operability " and " resectability " We can seldom forecast whether or not any operation is likely to be palliative We can sometimes reasonably hope from our experience that it may be so, but it is only at death or thereabouts that we can make a just appraisal When outlining treatment we must always try to bear in mind the likely behaviour of the tumour untreated, helped by what we know of its histology and of its observed growth to date Of the merit of resecting a fungating rectal growth I am convinced, in the presence of hepatic and even of pulmonary metastases We may not thereby prolong life (Modlin, Walker, 1949) but we do frequently and materially relieve distressing symptoms It is unhappily true, however, that all too often an operation planned to be palliative turns out to be no more than meddlesome, and seldom does the reverse hold true Before we embark on any attempt at palliative surgery we should first earnestly put to ourselves the question, " What are we endeavouring to palliate ? " just as we should see to it later on that we give an honest answer to the further question, " How far have we succeeded ? " Generally speaking, there can seldom be much justification for heroic palliative resections with a high risk of a complicated and tedious convalescence

(3) Following our wide resection the functional disability or the

deformity may be intolerable even to one who is lucky enough to have been cured of his disease Is it fair, for example, to rob a man of his tongue and jaw and to condemn him to a life of tube feeding ? What of the crippling which follows a hind-quarter amputation ? Is a wet colostomy compatible with a full life, or does it imply virtual social ostracism ?

To each of these questions we must have a reasoned answer, given with sympathy and understanding, bearing closely in mind the influence of such happenings on our own patient As Stammers (1949) so aptly put it " Life is quality, not quantity " Survival alone can never be enough , comfortable survival is the lowest standard by which we can be allowed to judge our success or failure

(4) There is one danger against which we must constantly be on our guard when we consider the place for heroic resections Increasingly every new problem will become a fresh challenge, which, be it from resolution or from pride, we feel bound to accept This should be all to the good, but I suspect that in the process our judgment may fail, and we may commit the grave sin of failing to appreciate our limitations in the battle for cure The cold verdict of the statistician helps much to curb such immoderate enthusiasm

Now it is apparent that these arguments are largely dependent on purely personal considerations—on a knowledge, not, for example, of what total glossectomy can achieve in the treatment of lingual cancer, but of what it has to offer to our own patient, to Mr Smith or Mr Jones For if in his management, there is any question of alternative methods of treatment, of a safe palliative procedure or of a hazardous attempt at wide resection for cure, the responsibility for the choice is only the surgeon's If he knows his own mind, and surely he ought to, he can never reasonably transfer the burden of choosing to his patient's shoulders And, in making the choice, he will do well to be influenced, no less by a fair and sympathetic appraisal of the patient who has surrendered himself into his care, than by the cold objective direction he receives from the pathologist, from follow-up results or from the cumulated experience of his colleagues Only in this way will we be able to recognise the adventurous but wise from the enthusiastic but unreasoning, the understanding from the uncompromising, the hero from the butcher

And finally, so long as the surgeon strives to improve the chance of cure in cancer, so he will tend continuously to widen his resection, and we would not have it otherwise But the limitations of any attack on cancer which depends for its success only on development in this direction, must be obvious , increasing endeavour is likely to earn only a diminishing return A consciousness of the limitations of surgical methods, however elaborate and however extended, will do us no good if it only damps our ardour and tempts us to give in, and valuable only if it leads to an intensification of efforts towards an understanding of the nature of malignant growth and of its complete control

REFERENCES

Abrams, H L, Spiro, R, Goldstein, N (1950), *Cancer*, 3, 74 Alexander, J, Haight, C (1947), *Surg Gynec and Obstet*, 85, 129 Allison, P R, Borrie, J (1949), *Brit Journ Surg*, 37, 1 Andreassen, M (1947), *Lyon chir*, 42, 702 Berne, C J, Freedman, M A (1951), *Amer Journ Surg*, 82, 5 Bowers, R F (1949), *Surgery*, 26, 523 Bricker, E M (1950), *S Clin North America*, 30, 1511 Brunschwig, A (1948), *Cancer*, 1, 177 Brunschwig, A (1949), *Ann Surg*, 129, 499 Carroll, W W (1952), *Surg Gynec and Obstet*, 94, 1 Cattell, R B, Warren, K W (1951), *New England Journ Med*, 244, 975 Coley, B L, Higinbotham, N L, Romieu, C (1951), *Amer Journ Surg*, 82, 27 Coller, F A, Kay, E B, McIntyre, R S (1941), *Arch Surg*, 43, 748 Dahl-Iverson, J (1951), *Journ internat chir*, 9, 492 Dahl-Iverson, J, and Andreassen, M (1949), *ibid*, 9, 27 Deddish, M R (*a*) (1950), *Proc Roy Soc Med*, 43, 1075 Deddish, M R (*b*), (1950), *New York State Journ Med*, 50, 2047 Deddish, M R (1951), *Cancer*, 4, 1364 Dunphy, J E (1950), *New England Journ Med*, 242, 167 Edgerton, M T (1951), *Cancer*, 4, 110 Eker, R (1951), *Acta chir Scandinav*, 101, 112 Farris, J M, Ransom, H K, Coller, F A (1943), *Surgery*, 13, 823 Gilchrist, R K (1950), *Surgery*, 27 787 Goligher, J C, Dukes, C E, Bussey, H J R (1951), *Brit Journ Surg*, 39, 3 Gordon-Taylor, G, Wiles, P (1935), *Brit Journ Surg*, 22, 671 Gordon-Taylor, G, Wiles, P, Patey, D H, Warwick, W T, Monro, R S (1952), *Journ Bone and Joint Surg*, 34B, 14 Grinnell, R S (1950), *Ann Surg*, 131, 494 Haagensen, C D, Stout, A P (1943), *Ann Surg*, 118, 1032 Halstead, W S (1907), *Ann Surg*, 46, 1 Handley, R S, Thackray, A C (1949), *Lancet*, 2, 276 Harvey, H D Titherington, J B, Stout, A P, Fordyce, B St J, (1951), *Cancer*, 4, 717 Kremen, A J (1951), *Surgery*, 30, 227 Lahey, F H (1950), *Surg Gynec and Obstet*, 90, 246 Lahey, F H, Marshall, S F (1950), *Ann Surg*, 132, 540 Lees, J C, Park, W W (1951), *Surg Gynec and Obstet*, 93, 129 Lefèvre, H (1947), *Rev de chir*, 148 Lefevre, H, Lortat-Jacob, J L (1950), *Journ chir*, 66, 670 Loggan, P B, Kleinsasser, L J (1951), *Surg Gynec and Obstet*, 93, 521 McNeer, G, Sunderland, D A, McInnes, G, Vandenberg, H J, Lawrence, W (1951), *Cancer*, 4, 957 McNeer, G, Vandenberg, H J, Donn, F Y, Bowden, L (1951), *Ann Surg*, 134, 2 McWhirter, R (1948), *Proc Roy Soc Med*, 41, 122 Meissner, W A (1949), *Journ Nat Cancer Inst*, 10, 533 Modlin, J, Walker, H S J (1949), *Cancer*, 2, 767 Pack, G T, Ehrlich, H E (1946), *Ann Surg*, 123, 965 Pack, G T, McNeer, G, Booher, R J (1947), *Arch Surg*, 55, 457 Pack, G T (1951), *Amer Journ Surg*, 17, 271 Pringle, J H (1908), *Edin Med Journ*, 23, 496 Saphir, O, Amromin, G D (1948), *Cancer*, 1, 238 Scott, H W, Longmire, W P (1949), *Surgery*, 26, 488 Seiler, H H, Clagett, O T, McDonald, J R (1950), *Journ Thor Surg*, 19, 655 Slaughter, D P, Roeser, E H, Smejkal, W F (1949), *Surgery*, 26, 507 Smith, F H (1947), *Surg Gynec and Obstet*, 84, 402 Stammers, F A R (1949), *Proc Roy Soc Med*, 42, 667 Stammers, F A R, Brain, R H F (1951), *Lancet*, 1, 1137 Sugarbaker, E D, Gilford, J (1946), *Surg Gynec and Obstet*, 83, 767 Sugarbaker, E D (1946), *Ann Surg*, 123, 1036 Sugarbaker, E D, Wiley, H M (1950), *Surgery*, 27, 343 Taylor, G W, Wallace, R H (1950), *Ann Surg*, 132, 833 Thomas, W D, Waugh, J M, Dockerty, M B (1951), *Arch Surg*, 62, 847 Walters, W, Gray, H K, Priestley, J T, Waugh, J M (1950), *Proc Staff Meet Mayo Clin*, 25, 136 Wangensteen, O H (*a*), (1949), *Trans Amer S A*, 67, 219 Wangensteen, O H (*b*), (1949), *Wisconsin Med Journ*, 48, 591 Wangensteen, O H (1950), *Surgery*, 27, 944 Ward, G E, Robben, J D (1951), *Cancer*, 4, 98 Warren, S (1933), *New England Journ Med*, 209, 825 Welch, C E, Giddings, W P (1951), *New England Journ Med*, 244, 859 Whipple, A O (1938), *Amer Journ Surg*, 40, 260 Wright, C J E (1949), *Journ Path and Bact*, 61, 507 Verbrugghen, A (1931), *Proc Staff Meet Mayo Clin*, 6, 765

POST-PARTUM BLOOD PRESSURE LEVELS

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THE occasional occurrence of unexpected hypertensive phenomena in the immediate post-partum period suggests that in some patients the stability of the blood pressure may be markedly affected by the process of labour

The regular recording of the blood pressure during pregnancy is now an established practice Blood pressure levels during labour have been investigated from time to time, and it is known that a transient rise occurs during the uterine contractions, most markedly in the second stage There is, however, very little evidence to show the effect of labour as a whole on the blood pressure level, and no published record of it at the end of the third stage Current textbooks make scant reference to it, and a fairly extensive search of the literature failed to reveal any paper on the subject apart, of course, from those in which the blood pressure level is used to check the patient's general condition in cases of shock or hæmorrhage

This investigation was therefore planned in an attempt to find out, firstly, whether labour has any uniform effect on the blood pressure, and, secondly, whether there are any cases in which unexpected hypertension does occur It has been the practice in this department to record the blood pressure within an hour of the completion of labour irrespective of the patient's previous clinical condition, and an analysis was undertaken of the delivery records between 30th June 1948 and 1st July 1950

MATERIAL

In the two-year period 2863 patients were delivered, and of this number 862 cases had no record of the post-partum blood pressure readings The loss of this number of records does not invalidate the statistical results of the analysis since the incomplete records are scattered evenly throughout the series and the effect of their loss is minimal The general conclusions, therefore, drawn from the analysis of the remaining 2001 cases are valid

Since so many factors influence the blood pressure it was difficult to establish the maximum limit of normality, but after due consideration it was decided to accept 140/90 as the upper limit of normal, and any case showing a post-partum blood pressure reading higher than this was included

Of the 2001 cases analysed, 1758 (87 7 per cent) were found to have normal blood pressure readings after delivery was complete, and 243 (12 3 per cent) were found to have hypertension by the standard referred to above

Clearly a proportion at least of the 243 cases of post-partum hypertension would be cases of toxæmia or hypertension in which the raised blood pressure of the antenatal period was carried over into the puerperium The group, therefore, was analysed for evidence of antepartum hypertension and 126 cases were found (51 9 per cent) In addition 11 cases (4 5 per cent) were found to have incomplete antenatal records The remaining 106 patients (43 6 per cent) were those in whom there was no hypertension during pregnancy or at the beginning of labour, and in whom the immediate post-partum hypertension was completely unexpected This last group represents 5 3 per cent of the whole series of 2001 cases

ANALYSIS

Further investigation of these cases seemed desirable, and a study of the clinical histories showed that the degree of hypertension was not gross in the majority , the following table shows the distribution at various levels of blood pressure

140/90 -150/100 mm Hg	81 cases
151/101-170/120 mm Hg	21 ,,
Above -170/120 mm Hg	4 ,,

In the majority of the patients daily blood pressure recordings were not made in the puerperium, but in the 4 highest the charts show a steady fall during the first five days after delivery Treatment was not recorded except in the highest group, and in these it followed the orthodox line of morphia followed by phenobarbitone, low salt diet and complete rest in bed

The progress of these cases, therefore, can only be judged by the blood pressure recordings on discharge from hospital and at the follow-up examination in the Post-natal Clinic eight weeks after delivery On discharge from hospital the distribution of cases according to the height of the blood pressure, was thus —

Below -140/90 mm Hg	58 cases
140/90 -150/100 mm Hg	11 ,,
151/101-170/120 mm Hg	12 ,,
Above -170/120 mm Hg	5 ,,

From this table it would appear that the degree of hypertension ten to fourteen days after delivery was rather more severe in many cases than immediately after delivery, but account must be taken of the emotional instability of puerperal patients, particularly when faced with an examination by the doctor on which their discharge from hospital depended This probably accounts for a large number of the hypertensive records at this examination, but the hypertension is transient and many of the patients undoubtedly belong to the large group of the population who have a labile blood pressure

A true picture of the progress is gained by study of the blood pressure records at the Post-natal Clinic Here it was found in the group under analysis, the cases were distributed thus —

Below -140/90 mm Hg	79 cases
140/90 -150/100 mm Hg	Nil
151/101-170/120 mm Hg	1 case
Above -170/120 mm Hg	1 ,,
No record	25 cases (These represent cases who did not attend the Clinic)

It is thus apparent that in only a small percentage of patients is the unexpected immediate post-partum hypertension an indication of a truly hypertensive state, and in this small number a much longer follow-up would be needed to establish that hypertension was permanent

An attempt has been made by further analysis of the whole series of 106 patients to find some common ætiological factor to account for the unexpected hypertension

(1) *Age* —Age appears to throw some light on the problem The distribution was recorded in age groups according to the following table —

	Puerperal hypertension	Antenatal hypertension
(1) Under 20 years	6	7
(2) 20 to 30 ,,	72	67
(3) 30 to 40 ,,	24	46
(4) Over 40 ,,	4	6

It is clear that by far the greater number fall into the twenty to thirty age group, and if this fact is assessed in conjunction with an analysis by the same age groups for the cases with established antenatal hypertension, it will be seen that the ratio is approximately the same in both series In the former 1 12 4 1 and in the latter 1 9 6 1 Thus unexpected puerperal hypertension occurs most frequently in patients whose ages fall into those groups which show the highest incidence of toxæmia of pregnancy This is suggestive of a toxæmic origin for rise in blood pressure after labour in patients apparently normal

(2) *Parity* —If the suggestion made under consideration of the age groups is true then anaylsis for parity should show a preponderance of primiparæ Of the 106 cases 57 were primiparæ and 49 multiparæ, the preponderance therefore is slight, but it does support the suggestion though not so strongly as might be expected

(3) *Maturity* —For this analysis the cases were divided into three groups —

(1) Those who came into labour within four weeks of the expected date

(2) Those who were delivered at term

(3) Those who were delivered up to two weeks after the expected date

In these three categories there were 35 premature, 50 full term and 21 who went into labour after the expected date It appears, therefore, that the duration of the pregnancy also supports the suggestion that the unexpected hypertension may be delayed toxæmic phenomenon, since premature onset of labour is a common finding in toxæmia of pregnancy, and a proportion of 35 premature to 50 full term deliveries in a series of 106 cases is much above the average.

It seemed reasonable also to assess the possible effect of labour upon the blood pressure, and in order to do this the series was analysed for length of labour, type of delivery, use of anæsthesia and third stage complications

(1) *Length of Labour* —Ninety-one of the cases were found to have had a total duration of labour of less than twenty-four hours it is therefore clear that prolongation of labour does not result in elevation of blood pressure, and indeed one would not expect it to do so, for such patients are in a state of physical exhaustion when the blood pressure tends to be low Of the remaining cases 10 had labours up to forty-eight hours in duration, 5 over forty-eight hours and there was one elective Cæsarian section

(2) *Type of Delivery* —Ninety-eight of the deliveries were normal, 4 were forceps deliveries, 3 were twin deliveries, and one was an elective Cæsarian section Instrumental delivery therefore plays no part in this problem This is borne out by the next factor

(3) *Anæsthesia* —One hundred of the patients had no form of surgical anæsthesia, the remaining 6 having general anæsthetics Analgesia was used in all cases of normal delivery, pethidine and chloral being the drugs in common use, and gas/air and trilene inhalations only at the end of the first stage and during the second stages

(4) *Third Stage Complications* —Of the 106 patients under review only 9 are recorded as having a post-partum loss of blood between 10 and 20 ounces, and only in one case was the placenta removed manually, the reason being failure to separate, without hæmorrhage This last patient developed hypertensive cardiac failure following the manual removal and died Autopsy revealed a large suprarenal tumour

It therefore seems clear that the type of labour and delivery have little, if any effect, on blood pressure even in the immediate post-partum period

DISCUSSION

It appears from the investigation of these 2001 unselected patients that immediately after delivery the blood pressure remains within normal limits in the majority of cases. In the cases where it is found to be raised, approximately half show an antenatal hypertension which anticipates a post-partum reading above the normal, but in the remainder there is no previous abnormality of the pregnancy and the finding is unexpected.

In discussions on post-partum eclampsia the validity of the diagnosis has been questioned, and the view has been taken that when post-partum eclampsia occurs there has been an ante-partum toxæmia which has been missed. It now seems clear that such may not be the case and that hypertension may occur *de novo* immediately following labour. This is probably the explanation of the occasional case of unexpected hypertensive cardiac failure following labour. Since these two serious complications occur, even though infrequently, it seems reasonable to suggest that routine recording of the post-partum blood pressure should be made at the same time as the pulse and temperature.

The explanation of this sudden rise in blood pressure is not clear. The analysis of the cases in this series did not reveal any factor in the labours which would predispose to such a finding, but it is worth noting that prolonged or difficult labours which leave the patient exhausted were conspicuously absent, and that the finding was made almost entirely in young patients who had had normal labours. The most likely possibility is that the condition is a manifestation of sub-clinical toxæmia which is brought to light by the strain of labour in patients whose blood pressures are unusually labile. As has been shown, the majority of patients who show this rise in blood pressure have no other accompanying clinical symptoms or signs, and their progress with usual methods of treatments is good. The frequency, however, with which the condition occurs (1 : 20 cases) and the possibility of the more serious conditions of post-partum eclampsia and hypertensive cardiac failure arising seems to justify a more careful watch on the blood pressure immediately following delivery than is at present usual. A further analysis is required to confirm or modify the findings of this paper, and this is being undertaken.

SUMMARY

(1) Two thousand and one records of delivery were examined for blood pressure recordings immediately after labour. One thousand seven hundred and fifty-eight were found to be within normal limits and 243 (12.3 per cent.) to be raised.

(2) Of the 243 cases in the hypertensive group 126 were found to have evidence of ante-partum hypertension, 11 had incomplete records and 106 (43.6 per cent.) had no evidence of any rise in blood pressure either in pregnancy or at the beginning of labour.

(3) The 106 cases (5 3 per cent of the whole series) of unexpected post-partum hypertension were analysed for the type of labour and for the general factors of age, parity and maturity No common ætiological factors were found

(4) Follow-up of the cases showed that in the majority (at least 75 per cent) the hypertension had disappeared in two months without special treatment

(5) A suggestion is made that this may be a manifestation of sub-clinical toxæmia

(6) In view of the occasional occurrence of post-partum eclampsia and hypertensive cardiac failure, it is suggested that the result of the investigation justifies and necessitates routine recording of the blood pressure at the end of labour

We are indebted to Mr Linton Snaith for permission to use the case records quoted in this paper

OBSERVATIONS ON THE PLASMA FIBRINOGEN CONTENT AFTER MYOCARDIAL INFARCTION

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FIBRINOGEN is one of the proteins normally present in plasma, and is constantly utilised within the body In the healthy adult approximately 6 g are synthesised by the liver and are metabolised each day (Everett, 1946) Much larger quantities are formed in the presence of inflammation, which with injury is the most powerful stimulus to fibrinogen production The stimulus does not depend on bacterial products, as sterile or aseptic inflammatory processes have the same effect Meyers (1948) has shown that myocardial infarction is followed by a rise in plasma fibrinogen He suggests that determination of the fibrinogen levels in the plasma may be a valuable guide to the progress of the reparative process in the infarcted area The present investigation was undertaken to determine (*a*) the frequency with which increase in the plasma fibrinogen content occurs after a coronary thrombosis, and (*b*) the relation, if any, of the clinical severity of the case with the degree and duration of the changes observed

MATERIAL

Forty-two patients were studied during forty-five attacks of coronary thrombosis—33 males, 3 of whom have been observed during two attacks, and 9 females All were inpatients in the Royal Infirmary, Edinburgh, and all showed electrocardiographic evidence of recent myocardial infarction Serial estimations of plasma fibrinogen content were carried out at frequent intervals during the period of hospitalisation Seven patients were treated conservatively, while anti-coagulants were employed in the remaining 38 patients Seven deaths occurred during the period of observation, 2 of these patients were treated conservatively, and 5 received anti-coagulants In addition, plasma fibrinogen estimations were carried out on 10 healthy male adults as controls, and to establish the normal for the method used

METHOD

Blood samples were collected at 9 a m each day, except on the day of admission A clean venepuncture was performed, blood was withdrawn into a dry sterile all-glass syringe and was immediately transferred to a specially prepared glass tube graduated at 6 ml and containing the optimum amount of oxalate—30 mg. to 6 ml. of blood.* Thorough mixing of the oxalate powder with the blood was ensured by corking the tubes and inverting gently several times. Hæmolysis was avoided.

Fibrinogen was estimated by the following method. To 2 ml. of plasma there were added 30 ml. of 0.9 per cent. sodium chloride and 1 ml. of 2.5 per cent. calcium chloride, and the mixture was incubated overnight at 37° C. The clot which had formed was collected on a fine glass rod and dried on a filter paper, care being taken that none was lost. The nitrogen content was estimated by the micro-kjeldahl method, and the fibrinogen content calculated using the factor 6.25. The accepted figures for the normal range of plasma fibrinogen is between 0.2 and 0.4 g. per cent. In the 10 control cases investigated the results obtained by the method above varied from 0.24 to 0.32 g. per cent.

TABLE I

This Illustrates the Distribution of the Maximum Plasma Fibrinogen Levels Observed in 32 Patients with a Recent Coronary Thrombosis, and their Relationship to the Severity of the Attack as Divided Clinically into Three Grades, Mild, Moderate and Severe

Maximum Plasma Fibrinogen	Number of Cases of Coronary Thrombosis			
	Total	Clinical Assessment		
		Mild	Moderate	Severe
0.30 0.39 g. per cent.	1	1		
0.40 0.49 ,,	3	2		1
0.50 0.59 ,,	10	9	1	
0.60 0.69 ,,	9	5	2	2
0.70 0.79 ,,	6	1	3	2
0.80 0.89 ,,	1		1	
0.90 0.99 ,,	2		1	1
Total	32	18	8	6

DISCUSSION

The time after the acute attack at which the patients first came under observation varied widely: thus 3 cases were already in hospital at the time of their coronary occlusion, while, at the other extreme, one patient was not admitted until twenty-two days after the infarct had been sustained. The cases studied fall into two groups: (*a*) 32 patients investigated from within one to five days after the onset, and (*b*) 13 patients admitted between the eighth and twenty-second day after the infarct. In 30 of the 32 cases in group (*a*) the plasma showed a rise in fibrinogen content to abnormally high levels during the first or second weeks after the myocardial infarction, the highest recorded level being 0.98 g. per cent. From Table I it will be seen that in the majority of cases the maximum figure lay between 0 50 and 0 79 g per cent In the remaining 2 cases of this group the highest levels were at the upper limit of normal, viz , 0 39 and 0 40 g per cent respectively Since in these patients the first estimations of fibrinogen were lower, a minor rise did occur Six patients were examined on the day of the attack, 11 on the second day and 15 between the third and fifth day after the infarct occurred Of the 6 patients seen on the first day, 3 were examined within three to six hours after the onset and at that time showed normal fibrinogen levels The other 3 patients were not examined till ten to seventeen hours had elapsed and these all showed abnormally high levels Of the 11 patients seen for the first time on the second day, all had plasma fibrinogen levels above the normal range, while of the remaining 15 patients examined for the first time between the third and fifth day after the acute incident, only 3 gave first readings still within the normal range, viz , 0 36 and 0 38 and 0 39 g per cent respectively These figures are near the upper limit of the normal range and may have been high for the patients in question, so that the rise though slight may have started

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* These tubes were prepared by adding 0.5 ml. of 6 per cent. sodium oxalate to each tube and drying them in an oven at 100° C. till the oxalate remained as a powder.

TABLE II

The Day on which the Maximum Plasma Fibrinogen Level was Recorded in 32 Cases of Coronary Thrombosis, is Shown

Day After Onset	Number of Cases	Day after Onset	Number of Cases
2nd	2	9th	1
3rd	3	10th	0
4th	3	11th	2
5th	7	12th	2
6th	5	13th	0
7th	4	14th	2
8th	1	15th	0

The times at which the highest levels occurred and the subsequent fall started varied considerably in different patients Reference to Table II will show that the common peak period lay between the fifth and the seventh day after the attack In a few cases the highest level was attained more slowly and occurred between the tenth and the fourteenth day of the illness As the samples of blood for estimations were not withdrawn every day but with a few days' interval between, it is possible that in some cases the highest level of plasma fibrinogen reached may have been missed This must be borne in mind when considering the results It would appear, however, that in general there is a rapid rise in plasma fibrinogen to a maximum during the first week after the infarct occurs

In all the cases studied this steep rise in the early stages of the disease was succeeded by a gradual return of the plasma fibrinogen levels to within normal limits during the succeeding weeks This is illustrated in Fig 1 The fall occurs over a varying period of time Excluding the 2 patients who showed only a slight rise within the limits of normal and 5 patients who died during the first few weeks, 25 cases remain for analysis Nine of these showed a return of the plasma fibrinogen to within the normal range during their stay in hospital, *i e* within six weeks after the attack The duration of the abnormal levels in these patients ranged from fifteen to thirty-six days after the occurrence of the coronary thrombosis The maximum level attained was under 0 6 g per cent in 6 of the 9 cases, and was lower than that reached in the other 16 cases of the group under consideration These 16 cases had not only a higher maximum level—only 3 showed a figure under 0 6 g per cent—but the return to normal was much slower The final reading prior to discharge from hospital was still above the normal level Nine of these 16 cases have been followed up six weeks after their discharge from hospital, *i e* they were under observation for three months after the coronary thrombosis had occurred Five had returned to normal plasma fibrinogen levels at that time, and 4 were still above normal, viz 0 41, 0 43, 0 44 and 0 49 g per cent respectively As already stated 5 of the patients died, 4 in congestive

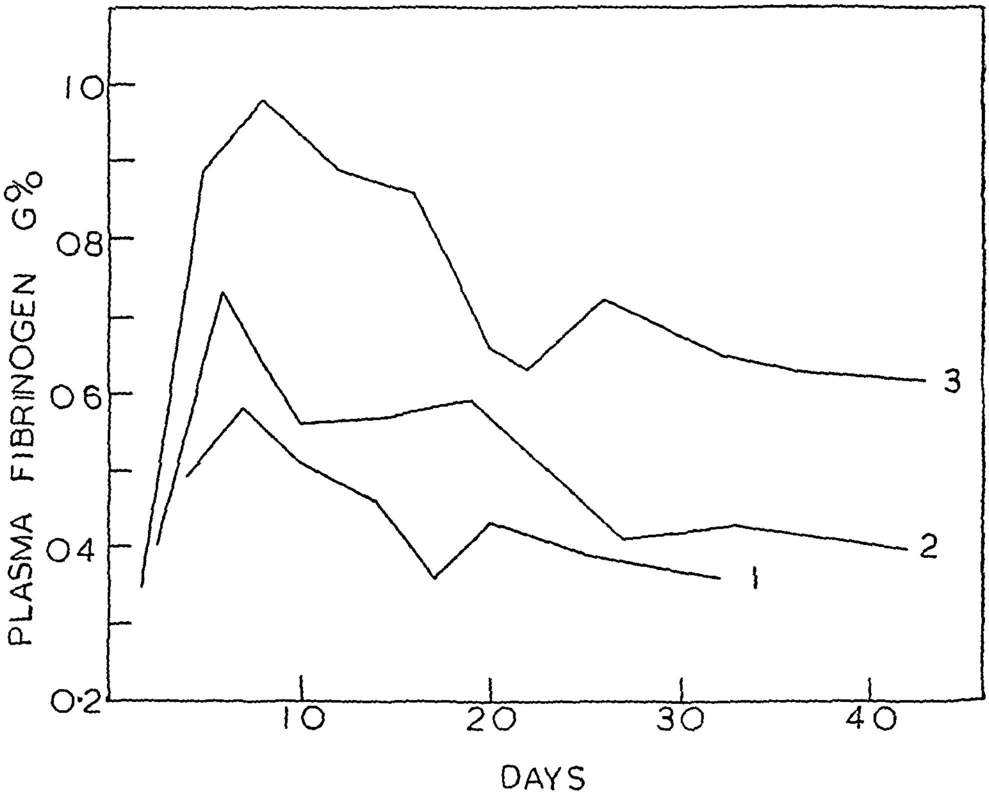

FIG 1 —The changes in plasma fibrinogen content observed in 3 cases of coronary thrombosis are illustrated The extreme variation in the magnitude of the increase in plasma fibrinogen and its duration are well known Clinically Case 1 had a very mild attack, Case 2 was moderately severe, while Case 3 was seriously ill

heart failure and 1 suddenly and unexpectedly In these cases the serial levels of fibrinogen did not differ materially from those obtained in the patients who survived

Comparison of the rise in plasma fibrinogen levels with the severity of the coronary thrombosis—the latter being assessed on clinical grounds in all cases by the same physician—shows that the more severe attacks tend to be associated with the higher levels of fibrinogen in the plasma (Table I) Determination of blood sedimentation rate was done throughout the course of the illness in all the patients, and it was found that in most cases the B S R changed in a fashion roughly parallel with the rise and subsequent fall in fibrinogen The closeness of the correlation has not, however, been mathematically examined Fig 2 illustrates this point, the curves shown by these two factors tend to be parallel to each other, although the fall in plasma fibrinogen may lag behind that of the B S R Comparison of individual cases shows that a particular plasma fibrinogen level is not associated with a particular B S R reading and *vice versa*, thus a B S R of over 100 mm/hr has been observed with plasma fibrinogen levels of 0 63 and 0 43 g per cent, while B S R s of approximately 50 mm/hr occurring two weeks after the infarct have been associated with plasma fibrinogen levels ranging from 0 41 to 0 78 g per cent

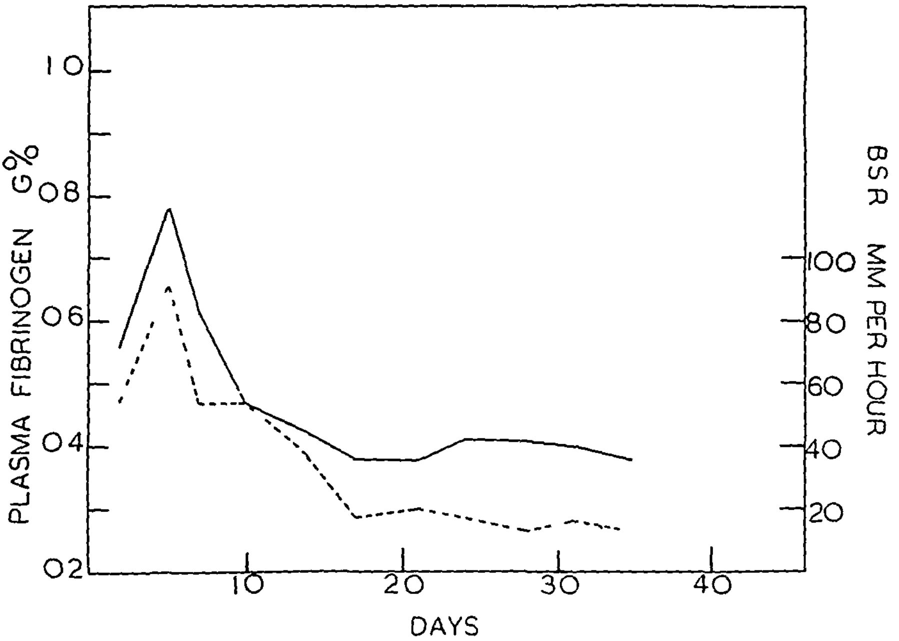

FIG 2—Serial observations made on the plasma fibrinogen content (continuous line) and on the blood sedimentation rate (dotted line) in one moderately severe case of coronary thrombosis are illustrated

The 13 patients in group (*b*) were first investigated between the eighth and twenty-second day after the coronary thrombosis was sustained These have been analysed separately One patient died on the twelfth day, while 12 survived All received tromexan All but one showed abnormally high plasma fibrinogen levels from the beginning of examination Eleven patients admitted between the eighth and nineteenth days showed a rise in plasma fibrinogen level during the first few days of their investigation, the increase observed varying from 0 03 to 0 27 g per cent The maximum level was observed on the twelfth and thirteenth days after the infarct in 3 patients , on the seventeenth day in 2 , and between the twentieth and twenty-fourth days in 6 cases Thereafter the fibrinogen levels fell gradually towards normality Two cases admitted on the thirteenth and twenty-second days respectively showed no such initial rise in fibrinogen content during the first few days after admission As in group (*a*) one-third (4 of the patients) showed plasma fibrinogen levels within the normal range in twenty-four to thirty-six days after the infarct, while two-thirds (8 patients) still showed fibrinogen levels greater than 0 40 g per cent at the time of their discharge from hospital Three of these latter 8 patients have been examined six weeks after their discharge, and in 2 the fibrinogen levels were still high, being 0 40 and 0 41 g per cent respectively

The fibrinogen estimations recorded in the patients in group (*b*) differ in one important respect from these obtained in the group (*a*) patients The rise in plasma fibrinogen content in the 11 patients described above occurred at a time when, in the group (*a*) patients, the fibrinogen levels had begun to fall Some factor other than the myocardial infarct, and common to all cases would therefore appear to be involved Tromexan administration may be this factor, as all cases were so treated Dicoumarol is known to influence fibrinogen production by the liver (Irish and Jaques, 1945), temporarily stimulating fibrinogen production when administered in moderate dosage, and damping down fibrinogen production when given in massive dosage It is therefore possible that tromexan administration in therapeutic dosage may temporarily stimulate fibrinogen production by the liver This is at present under investigation In the group (*a*) patients who received tromexan (24 cases) or dicoumarol (1 case) this effect of the coumarol drug may be overshadowed by the more powerful stimulus of the myocardial infarct The 7 patients in group (*a*) who were treated conservatively differed in no respect from those receiving anti-coagulants, except in so far as the maximum level recorded did not exceed 0 79 g per cent The numbers involved are too small to draw definite conclusions

SUMMARY

An increase in plasma fibrinogen content occurs after myocardial infarction The maximum increase is detected about one week after the acute episode, and is succeeded by a gradual fall in plasma fibrinogen

levels In one-third of all cases, the level has returned to within normal limits by the sixth week after the onset, but in the remaining two-thirds, the readings are still abnormal at this time Plasma fibrinogen estimation may therefore be an additional aid in establishing in retrospect the diagnosis of coronary thrombosis In some cases the levels may still be abnormally raised three months after the acute incident The more severe cases tend to show the greatest rise in plasma fibrinogen, and in these a longer time elapses before a normal level is restored Patients observed from the onset react similarly whether treated conservatively or with anti-coagulants Patients first treated with anti-coagulant therapy from the eighth day after the attack, or later, show a further rise in plasma fibrinogen content from an already abnormally high level This may be related to tromexan administration

All patients were under the care of Dr A Rae Gilchrist We are indebted to him for permission to carry out the investigation, and also to Dr C P Stewart for the laboratory facilities provided

REFERENCES

EVERETT, M R (1946), *Medical Biochemistry* Second Edition, pp 70, 414
MEYERS, L (1948), *Arch Int Med* , 82, 419
IRISH U D , and JAQUES L P (1945), *Amer Journ Physiol* , 143, 101

NEW BOOKS

Statistics for Medical and other Biological Students By L BERNSTEIN, B SC, M R C S, L R C P, and M WEATHERALL, M A, D M, B SC Pp xii+180, with 17 figures Edinburgh E & S Livingstone 1952 Price 18s net

The practical usefulness of a knowledge of mathematics in medicine, and particularly in medical research, has long received inadequate recognition, and this is an attempt to correct the fault The authors are scientists, lecturers in physiology and pharmacology, and they have a sound knowledge of the needs of the medical man Descriptions of the various essential methods are full, simple and understandable Typical problems are given and worked out in detail so that the various steps can be readily followed Tables of squares, square roots, logarithms and other useful aids are included, so that the book can be used as a guide to the solution of practical problems This is an attractive little volume and should become popular

An Atlas of General Affections of the Skeleton By SIR THOMAS FAIRBANK, D S O, O B E, M S, ETC Pp xx+411, with 510 illustrations Edinburgh E & S Livingstone Ltd Price 55s net

The interest and great experience of Sir Thomas Fairbank in skeletal conditions is so well known that the advent of this textbook has been eagerly awaited

In the introduction there is given a classification of the various affections according to their etiology, so far as this is known, and this order has been followed throughout the book This etiological classification is—congenital developmental errors, acquired affections of unknown origin, those due to diet and metabolism, endocrine errors, infections, errors of the hæmopoietic and lymphatic systems, and multiple neoplasms There are still many cases which cannot be placed in a recognised group, but so far as this complex subject can be classified the author does it, and nobody could do it better There are some very helpful tables on such differential diagnostic features as blood chemistry, dwarfism, increased density of bone, and vertebral collapse It is obvious, therefore, how very helpful such a book is to the clinician

Most of the conditions, and particularly the rarer ones, are illustrated by individual cases given in detail The descriptions of the affections of the reticulo endothelial system are very complete and helpful, and the author points out the intimate relationship of this group of conditions on account of the fundamental pathology common to all There is no attempt to suggest treatment in any part of the book, as one would expect since so often there is none

The book is copiously illustrated and the pictures and the X-rays are extraordinarily well produced It is a classic and will be much cherished by those who own it

Text Book of Ophthalmology Vol V By Sir STEWART DUKE-ELDER, K C V O Pp xxxii+*5713 with 1181 illustrations* including 32 in colour London Henry Kimpton 1952 Price 90s net

Each succeeding volume of Sir Stewart Duke-Elder's *Text Book of Ophthalmology* is eagerly welcomed by ophthalmologists all over the world and added to its predecessors to make an up to-date and exhaustive work of reference for clinical ophthalmologists and research workers alike

Vol V deals with the ocular adnexa, the lids, the tear passages and the orbit, affections of which can be the most perplexing in the whole field of ophthalmology

In many conditions of the eyelids the eye specialist has common ground with the dermatologist, and the numerous excellent pictures of such conditions are bound to prove a great help on many occasions

In the section on the tear sac one cannot altogether agree that the operation of dacryocystorhinostomy requires " a surgeon who is an adept at a somewhat tricky technique " It would be a pity if this did anything to discourage the wider use of this most successful operation

It is a pleasure to read Sir Stewart's easy, lucid writing, and the occasional historical reference or picture makes this volume much more than a solely scientific one

Hippocrates on Intercourse and Pregnancy Translated by T U H ELLINGER, SC D, M A Pp 128 New York Henry Schuman 1952 Price $2 50

The translator points out that most scholars agree that the author of these papers is not the great Hippocrates of Cos but some physician of the rival Cnidian school and that he wrote in the 5th century B C They appear in English for the first time Of the two papers, that "on the development of the child" is by far the more important and interesting, and it is surprising to learn how much was already known of the subject at that time

The author acknowledges help with the manuscript from a professor of Greek and a professor of the History of Medicine, and an introduction and a series of notes has been supplied by Dr A F Guttmader, professor of Obstetrics

This little book should be of interest to all medical men and particularly to those engaged in the practice of obstetrics

Cardiac Emergencies and Heart Failure By ARTHUR M MASTER, MARVIN MOSER and HARRY L JAFFE Pp 159, with 13 illustrations London Henry Kimpton 1952 Price 22s net

The authors hope this volume will be of value to general practitioners in dealing with the "acute heart" Much recommended therapy is outwith the facilities of general practice in this country Insufficient emphasis is given to dangers of new potent drugs recommended Thoroughly up to date, always stimulating and often provocative

Ciba Foundation Colloquia on Endocrinology Vol 1 Edited by G E W WOLSTENHOLME, O B E, M B, B CH Pp xx+315, with 13 pages of illustrations London J & A Churchill, Ltd 1952 Price 30s net

This is the first volume reporting the proceedings of colloquia arranged by the Ciba Foundation It has two parts, the first dealing with steroid hormones and tumour growth, and the second with steroid hormones and enzymes The parts are divided into sections, each containing a paper with references and the discussion which followed the paper Those invited to attend are distinguished workers from many countries and, as might be expected, the standards are high The Ciba Foundation is to be congratulated on its decision to allow a wider circle an indirect share in these valuable symposia

Rheumatic Diseases Based on the Proceedings of the Seventh International Congress on Rheumatic Diseases Edited by CHARLES H GLOCUMB, M D Pp xxiv+449, with 126 illustrations London W B Saunders 1952 Price 60s

This volume has been prepared from papers or abstracts of papers presented at the Seventh International Congress on Rheumatic Diseases held in New York in 1950 The book is arranged so that papers dealing with various aspects of one subject or disease are grouped together Both the clinician and the research worker will find much to interest them The effect of cortisone and of A C T H on rheumatoid arthritis and acute rheumatic fever were first reported in detail at this conference by Hench and his colleagues, an event of historic importance in the field of clinical research It is a pity that there should be a delay of two years in publishing these papers, as much of the work reported has been published elsewhere in the interval

Called to Serve By PAUL GLIDDON and MURIEL POWELL Pp 127 London Hodder and Stoughton 1952 Price 7s 6d net

The doctor, the nurse and the chaplain each has a part in tending the sick, and this book describes the common foundation on which these professions are built, emphasises their vocation and shows how each is complementary to the other A helpful and stimulating book well worth reading by all who are Called to Serve

Surgical Forum—American College of Surgeons By Committee of Surgical Forum Pp xxxiii+667, with 290 illustrations London W B Saunders, Ltd 1952 Price 50s net

This volume presents the proceedings of the Surgical Forum of the Clinical Congress of the American College of Surgeons, 1951 More than 100 short papers are published in full and others are abstracted, these cover a wide field of surgery and experimental work related to surgery, and fully justify the claim made by Dr Owen Wangensteen in his Foreword that " the progress of surgery in America from year to year will be documented and reflected in these volumes " Most of the well-known surgical centres in America are represented by reports of research works and all the contributions are brief and readable British surgeons will find here an acceptable answer to the question, " What's new in America ? "

Elementary Medical Statistics By DONALD MAINLAND, M B, CH B, D SC, F R S E, F R S C Pp 327 Philadelphia and London W B Saunders Company 1952 Price 25s

This excellent book is highly recommended to all medical workers and students as simple to follow, interesting and instructive It has a special appeal to the medical practitioner, though it covers all the basic practices of statistics The author addresses himself to an audience interested in interpreting and evaluating medical experience —an audience whose needs he thoroughly understands and fully satisfies He shows the theoretical aspects involved in forming judgments and works out all the practical steps required in every kind of investigation or experiment The planning of the collection of data and the obtaining of a suitable sample are as fully explained as are the methods of analysis Each chapter is full of examples and illustrations of many different types of investigation to guide every kind of reader The common fallacies which lie behind " controlled " experiments, " impressions " from small samples, and clinical comparisons are also carefully studied

The good points of this book are manifold Introducing each chapter are valuable suggestions for the order of reading and possibly omission The important and fully explained distinction between enumeration data and mensuration data will be of the greatest help to practitioners The attention given to discussion of small difficulties and concepts too often glossed over is outstanding

The book is written simply, documented fully, explained clearly and carefully and designed to hold the interest both of the novice and of the more experienced The principles so ably expounded in the text will help practitioners in their work and in forming judgments of it The author has indeed fulfilled his objectives of presenting statistics as a fundamental science and of proving the value of statistical thinking in clinical medicine

Diseases of the Ear, Nose and Throat By G PORTMAN, M D Pp viii+728, with 666 figures London Baillière Tindall & Cox 1951 Price £7, 10s net

George Portman is well known for the post-graduate course in Otorhinolaryngology he conducted before the War This book is based on the lectures and instructions he gave and is unique in the speciality Prime place is rightly given to the clinical examination of the patient, special diagnostic procedures are kept in their correct prospective In this country many of the tests described under the examination of the auricular apparatus would be considered out of date and redundant, the omission of the Hallpike differential cold caloric test is an example The section on endoscopy reflects the continental school of thought predominantly, and the diverse methods described may be a little confusing to the student The sections dealing with anatomy and radiography and the interpretation of X ray films call for special praise

The publishers have to be congratulated upon the excellence of the illustration and plates, the translators, however, could have extended, with benefit, their activities to some of the explanatory data of the drawings This book can be confidently recommended to all students of the speciality who wish to acquire a sound clinical and diagnostic technique

NEW EDITIONS

Diseases of the Nervous System By F M R WALSHE Seventh Edition Pp xvi+365, with 63 illustrations Edinburgh E & S Livingstone 1952 Price 24s net

This magnificent book is unique in expressing both the distinguished author's personality and the common nervous disorders in a manner comprehensible to practitioners and senior students, for whom it is intended

One welcomes the way in which it stresses the importance of adequate history taking and clinical observation in this rather laboratory-minded era

Several sections contain new material and represent an admirably balanced interpretation of the most recent advances in the subjects considered This has not, however, diminished the original freshness of approach

The illustrations are excellent, the index thoughtfully compiled and the general production of a high standard

Recent Advances in Medicine By G E BEAUMONT, M A, D M, F R C P, D P H, and E C DODDS, D SC, PH D, M D, F R C P, F R I C, F R S (EDIN), F R S Thirteenth Edition Pp xv+397, with 59 illustrations London J & A Churchill 1952 Price 27s 6d net

The thirteenth edition of this book contains new chapters on the collagen diseases, anti histamines and radio active isotopes Like the previous editions this book provides the postgraduate student with a concise yet detailed account of the main advances which are for ever taking place in medicine It is well written and is a most informative and useful little book

Massage and Remedial Exercises By NOEL M TIDY, M C S P, T M M G Pp viii+519, with 192 illustrations Bristol John Wright 1952 Price 27s 6d net

This book has now reached its ninth edition—a fact that proves its continued popularity with physiotherapy students

The present edition includes additional material on the arrangement of Group Exercises both for the young and aged, also sections on treatment of varicose and other ulcers by the Bisgaard method and on treatment of spastic paraplegias on the lines of Dr Guttmann's work at Stoke Mandeville It is a very complete textbook

Miss Tidy, while she attempts to move with the times and add some of the more recent advances in the physiotherapeutic procedures, would have been well advised to have omitted some of the more out moded forms of treatment The book would have been improved with considerable cutting

Textbook of Medicine By various authors Tenth Edition, edited by Sir JOHN CONYBEARE, K B E M C, D M, F R C P, and W N MANN, M D, F R C P Pp xii+912 with 31 illustrations and 31 X ray plates Edinburgh E and S Livingstone Ltd 1952 Price 37s 6d net

For the tenth edition of this already well known textbook, Sir John Conybeare has secured the assistance of Dr W N Mann of Guy's Hospital as co editor Their purpose is to provide within as small a compass as possible the essentials of medicine for students and practitioners Difficult as it may be to achieve this purpose in the midst of constant changes and new developments, the editors have produced a textbook for which only the highest praise is applicable It has the merit, rare among current British textbooks of being completely up to date Numerous sections, particularly those dealing with treatment, have been re written The continued success of " Conybeare " is assured

A Textbook of Clinical Pathology Edited by SEWARD E MILLER, M D Fourth Edition Pp xxvi+1060, with 208 illustrations London Bailliere, Tindall & Cox 1952 Price 68s 6d net

The fourth edition of this book has been completely rewritten Emphasis is given to the explanation of basic scientific facts and to the interpretation and evaluation of laboratory diagnostic methods Detailed descriptions of highly skilled technical analysis are omitted from this book which deals solely with the practical procedures that can be performed in the side-room of any ward The book is designed to give the medical student, postgraduate and teacher of clinical medicine an authentic source of basic scientific information and how to interpret this knowledge in the presence of disease

Atlas of Human Anatomy By F FROLINE, M BRODEL and L SCHLOSSBERG with a text by J F WILLIAMS New Edition Pp 88 with numerous illustrations in colour London Geo Allen & Unwin 1952 Price 16s net

This small and well-produced book is illustrated by drawings originally made for wall-charts and the figures though small are very full of detail The new edition has been supplemented by ten new charts of the endocrine system in colours and by a large number of scale drawings of microscopic appearances

The text is rather elementary in character and not detailed enough for the use of medical students but would be very suitable for the instruction of nurses, first-aid workers and the like

BOOKS RECEIVED

AINSWORTH, G C, B SC, PH D, F L S Medical Mycology (*Sir Isaac Pitman & Sons Ltd*)	15s
BARTON WRIGHT, E C, D SC, F R I C The Microbiological Assay of the Vitamin B Complex and Amino Acids (*Sir Isaac Pitman & Sons Ltd*)	18s
BETT, Dr W R The Infirmities of Genius (*Christopher Johnson Publishers Ltd, London*)	18s net
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Edinburgh Medical Journal

December 1952

THE CHEMOTHERAPY OF URINARY TUBERCULOSIS

By WM G WIMSETT, L R C P, L R C S I
Robroyston Hospital, Glasgow

AT Robroyston Hospital, in December 1948, a controlled trial was instituted of streptomycin therapy for tuberculous disease of the urinary tract This investigation, conducted under the auspices of the Tuberculosis Research Unit of the Medical Research Council, was concluded in December 1951 At the completion of the trial 137 patients had been studied Selection of the cases for streptomycin treatment was made from a statistically prepared list kept at the M R C offices Streptomycin has been given to 70 patients and 67 were selected as control cases

The patients were grouped into five categories —

Group 1—Unilateral renal tuberculosis Minor lesion without cystitis
Group 2—Unilateral renal tuberculosis Major lesion necessitating nephrectomy , cystitis
Group 3—Bilateral renal tuberculosis Nephrectomy for the more advanced lesion
Group 4—Tuberculosis occurring in the remaining kidney subsequent to nephrectomy for unilateral disease
Group 5—(*a*) Major bilateral tuberculous lesions ,
(*b*) Minor bilateral tuberculous lesions

Complete urological investigation was carried out on all patients whether treated by streptomycin or not The investigation was repeated after treatment and thereafter the patients were observed and reassessed at intervals of three months Tests for streptomycin resistance and assays of streptomycin levels were performed routinely Observation on toxic effects with particular reference to vestibular damage were also made

The patients treated by streptomycin were given one gramme daily in two 0 5 gm intramuscular injections for ninety days Controls and streptomycin treated patients received similar general medical treatment

Read at a Meeting of the Tuberculosis Society of Scotland held at Bangour Hospital, on 25th January 1952

In March 1950 a preliminary report was presented by Jacobs and Borthwick to the section of Urology of the Royal Society of Medicine This report was based on the study of 90 patients Streptomycin had been given to 46 and 44 had been used as controls At the completion of the trial a further 47 patients had been studied Analysis of the additional cases confirms the conclusions reached in the preliminary report

Broadly these conclusions were —The treatment has no effect on an established caseocavernous lesion By some process encouraging constriction there is a possibility that the focus, though itself remaining active, may become shut off A regression of the constriction, however, can occur Streptomycin therefore cannot be recommended to supplant surgery, and in clinical unilateral renal tuberculosis the diseased kidney should be removed, or, where possible, partial nephrectomy should be attempted

Its automatic employment in cases unsuitable for surgery is not advised Thus, when there is an advanced bilateral renal lesion or an advanced lesion in a solitary kidney, no improvement in the kidney lesion can be anticipated, and vesical contracture may be accelerated where cystitis was previously present

In Group 2 cases, that is cases for nephrectomy, cystitis, streptomycin may prove beneficial as an additional measure possibly before as well as after surgery In addition, it should afford some measure of protection against activation and development of the disease in the apparently healthy kidney This statement is given with reservation, however, for at the completion of the trial, in Group 1 cases, the contralateral kidney became tubercle positive in 3 out of 10 treated cases, whilst this occurred in only 3 out of 11 controls

Streptomycin does have a beneficial effect on secondary tuberculous cystitis, but this would appear to be relative to the presence and degree of disease in the upper urinary tract Thus in Group 2 cases, that is those with a unilateral renal lesion in whom the affected kidney has been removed, cystitis has cleared and the urine has become tubercle negative in an appreciably larger number of streptomycin treated cases than has occurred with controls In Group 5 cases, however, consisting chiefly of patients with well-established bilateral disease, no beneficial effect on the bladder resulted In the few cases in whom the bilateral lesions were minimal, the effect of streptomycin on the bladder has been good

Toxicity—As previously stated, particular attention has been directed towards the occurrence of vestibular damage For each case, whether receiving streptomycin treatment or control, routine vestibular function tests were performed before and at the completion of treatment The examinations were carried out under the direction of Dr John McKinlay, ear, nose and throat consultant to the hospital Complete details of the results obtained are not yet available, but the following observations can be made

The incidence of vestibular damage in streptomycin treated cases was high In a number of patients the damage was slight, having been detected only after routine tests In a small proportion of cases the disturbance was marked, and in one such case cochlear damage, giving rise to deafness, occurred Both the vestibular and cochlear damage were irreversible

Combined Streptomycin and P A S Therapy—The effects of combining streptomycin with P A S were investigated in 20 patients, 5 of whom had been previously treated by streptomycin The remainder, 15 in all, had received general medical treatment without streptomycin In each case the previous treatment had been given under the conditions of the M R C trial, and at the completion of the streptomycin or control period in every case further treatment was required

On admission to the original trial, the cases had been classified in groups in the following proportions —

Group 1—Three streptomycin , four controls , total seven
Group 2—Six control cases
Group 3—Two streptomycin , three controls , total five

The two remaining cases, both controls, were classified as Group 5

For the purposes of this investigation the results of the initial treatment in each group are compared with that of combined therapy In each case streptomycin, 1 gm daily intramuscularly in a single dose, was given for ninety days with P A S 15 gm daily in divided doses

Group 1 —The 3 patients after treatment by streptomycin, remained tubercle positive In one the pyelographic appearances of the affected kidney had improved After observation for a period of eight months, the two in which no change had occurred developed cystitis and involvement of the other kidney In one the original lesion had worsened

Following combined therapy the first case showed further pyelographic improvement, the urine became negative for tubercle bacilli, and had remained thus for a period of six months Of the two cases which had deteriorated, the cystitis had improved in both , in one the contralateral kidney had become tubercle negative, and the affected kidney was removed Three months later the urine was tubercle negative, the remaining kidney normal and no cystitis was present, this having been maintained for twelve months In the third case the contralateral kidney remained involved and further worsening of the original renal lesion had taken place

Summary—In the above, following combined therapy, one case showed further improvement which has been maintained for six months In another the bladder and contralateral kidney were improved and surgery for the original lesion resulted in improvement, which has been maintained for twelve months The course of the disease was not arrested in the last case

Control Cases—Of the 4 cases, all remained tubercle positive, one had developed cystitis and the remainder involvement of the other kidney In one of the latter, the original lesion had worsened and a minor lesion developed in the contralateral kidney

TABLE I

Group 1 *Streptomycin Cases After* 8 *Months' Observation*

Total	Urine Conversion	Cystitis Developed	Involvement of Other Kidney	Pyelographic Changes		
				I	W	U
3	0	2	2	1	1	1

After S and P A S

Total	Urine Conversion	Cystitis		Other Kidney			Pyelographic Changes		
		Imp	None	I	U	N S	I	W	U
3	1	2	1	1	1	1	1	1	1

I = Improved, W = Worsened, U = Unchanged, N S = No spread

After combined therapy, three were tubercle negative Of these one showed pyelographic improvement but has failed to return for follow-up examination The others showed no pyelographic improvement

TABLE II

Group 1 *Control Cases at the Completion of* 3-6 *Months' Control Period*

Total	Urine Conversion	Cystitis Developed	Involvement of Other Kidney	Pyelographic Changes		
				I	W	U
4	0	1	3		1	3

After S and P A S

Total	Urine Conversion	Cystitis		Involvement of Other Kidney			Pyelographic Changes		
		Imp	None	I	U	N S	I	W	U
4	3	1	3	2	1	1	1		3

I = Improved, W = Worsened, U = Unchanged, N S = No spread

and partial nephrectomy was undertaken Thereafter urine conversion in both cases has been maintained for over six months The

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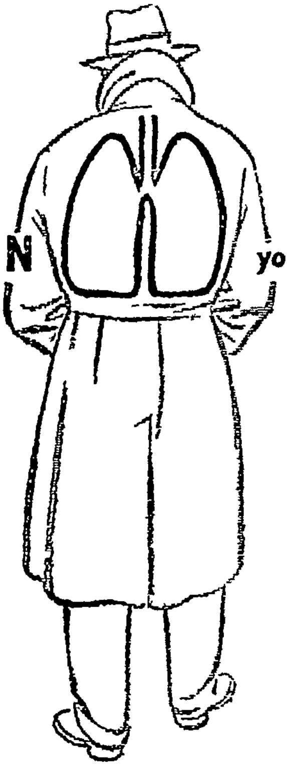

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fourth case, which remained tubercle positive, had shown bilateral pyelographic lesions following the control period

Summary—Of 4 cases, urine conversion was attained in three, pyelographic improvement in one, no change occurred in the last case

Group 2—Of the 6 patients in this group all remained tubercle positive following a control period No improvement in the degree of cystitis was noted and in two involvement of the other kidney had occurred

After combined therapy all became tubercle negative at the completion of treatment, the cystitis had improved in every case and no involvement of the other kidney was detected

TABLE III

Group 2 Control Cases at the Completion of 3 6 *Months' Control Period*

Total	Urine Conversion	Cystitis			Involvement of Other Kidney
		Improved	Worsened	Unchanged	
6				6	2

After S and P A S

Total	Urine Conversion	Cystitis			Involvement of Other Kidney
		Improved	Worsened	Unchanged	
6	6	6			

Summary—Marked improvement occurred in all cases and is maintained to the present, a period varying from two months in the last case to fourteen months in the earliest case

Group 3—Of the 5 cases in this group, two had been treated by streptomycin, but both remained tubercle positive after treatment In one the remaining kidney was improved but no improvement in the degree of cystitis resulted In both, bladder contracture had commenced

After combined therapy the lesions of the remaining kidney in both cases were improved One became tubercle negative, the other remained tubercle positive until the sixth month after treatment The urine conversion has been maintained in both for a further six months The degree of cystitis was difficult to assess as a result of increasing bladder contracture

Summary—The renal lesions in both cases were improved, urine conversion occurred at the completion of treatment in one case and in the other on the sixth month after treatment

Controls—Three cases all remained tubercle positive, no change was observed in the degree of cystitis and the lesion of the remaining kidney had worsened in one case

After combined therapy three were tubercle negative, the degree of cystitis and the disease of the remaining kidney were improved in each case At subsequent examination, after twelve months, one had become tubercle positive and deterioration of the renal lesion had occurred

TABLE IV

Group 3 Streptomycin Cases at Completion of Treatment

Total	Urine Conversion		Cystitis Unchanged	Other Kidney	
	Bladder	Kidney		Improved	Unchanged
2	0	1	2	1	1

After S and P A S

Total	Urine Conversion		Cystitis Unchanged	Other Kidney	
	Bladder	Kidney		Improved	Unchanged
2	1	2	2	2	

A second case has remained tubercle negative for fourteen months, but the filling defect in the affected kidney has reappeared Repeated cultures of urine, however, have failed to show tubercle bacilli In the third case no obvious disease was detected in the remaining kidney

TABLE V

Group 3 Control Cases at Completion of Control Period

Total	Urine Conversion		Cystitis			Other Kidney		
	Bladder	Kidney	I	W	U	I	U	W
3					3		3	

After S and P A S

Total	Urine Conversion		Cystitis			Other Kidney		
	Bladder	Kidney	I	W	U	I	U	W
3	3	3	3			3		

The urine remained tubercle negative but progressive bladder contracture necessitated uretero-colic anastomosis At operation a specimen of the kidney urine was obtained and found to be free from tubercle bacilli

Summary—Three cases after treatment were improved, urine conversion was maintained in one for twelve months The other two remain tubercle negative to the present, a period of fourteen months and six months

Group 5—Two patients were selected for this group, in one of whom the disease was advanced After the control period both cases remained tubercle positive, in neither had the cystitis improved nor had pyelographic changes occurred

After combined therapy one case was tubercle negative, the cystitis had improved but no pyelographic improvement was noted This has been maintained for six months In the other case the advanced bilateral lesions remained unchanged and rapidly progressive bladder contracture took place

TABLE VI

Group 5 Control Cases at Completion of Control Period

Total	Urine Conversion	Cystitis		Pyelographic Changes—None
		I	U	
2	0		2	2

After S and P A S

Total	Urine Conversion	Cystitis		Pyelographic Changes—None
		I	U	
2	1	1	1	2

I = Improved, W = Worsened, U = Unchanged

Summary—Two bilateral cases were treated, the worse showed no improvement, the less severe became tubercle negative and has remained so for the past six months

CONCLUSIONS

The results obtained, following treatment by combined therapy of the patients in this series, cannot be strictly compared with those of the streptomycin treated cases Of the 20 patients treated, 5 of these had received streptomycin at an earlier date, the remaining 15 general medical treatment However, with this imperfect basis for comparison, the case for combined therapy appears slightly better As in the case of streptomycin the established caseocavernous lesion responds poorly to treatment In 5 cases treated by combined therapy, however, urine conversion was attained, in 2 cases partial nephrectomy was performed during this tubercle negative phase and the conversion has been maintained for six months In one the lesion in the solitary remaining kidney was well established The urine in this case was rendered free from tubercle bacilli for a period of twelve months In the remaining 2 cases the lesions became shut off In one of these it has remained thus for six months, in the other the constriction has regressed after fourteen months but the urine remains tubercle negative

Combined therapy appears to afford a greater degree of protection to the contralateral kidney than does streptomycin In all cases in which spread to the other kidney was displayed by the presence of a tubercle positive urine, without an obvious pyelographic lesion, urine conversion was attained In other respects the results obtained were similar to those of the streptomycin treated cases It should be borne in mind, however, that every case, in both the M R C trial and in the above group, received general sanatorium treatment and, where indicated, an operation was performed It follows then, that neither streptomycin nor combined therapy is an alternative to prolonged sanatorium care or to surgery where conditions are favourable

Ljunggren has recently carried out a follow-up of patients operated upon for renal tuberculosis at the hospitals of Stockholm from 1934 to 1943 The results have yet to be presented in detail, but Ljunggren considers that the endeavour to improve the results of treatment by early diagnosis and early operation has not met with the success which was anticipated He suggests that early diagnosis should be followed by strict sanatorium treatment, chemotherapy and when the disease is in a more quiescent phase, surgery

As to the choice of chemotherapeutic agent, Ljunggren has attained some measure of success using P A S alone for prolonged periods Lloyd, Baumrucker and Stonington (1948) consider that streptomycin by itself has a very limited value and is not curative where there is a positive pyelogram In early tuberculosis, however, where the pyelogram is negative, it is considered to be of great benefit

Lattimer *et al* (1948) using streptomycin 1 8 gm daily for 120 days obtained a good response in early renal lesions, but where the renal disease, as shown by pyelography, is marked, the author considers that nephrectomy should be performed

In my opinion it is not unreasonable to expect an enhanced result from a combination of both drugs The small series of patients treated in Robroyston Hospital in this fashion offers some evidence in support of this

Ross *et al* (1951) has reported in a review of 51 cases the effect of (1) streptomycin , (2) streptomycin and P A S , (3) streptomycin and P A S alternatively , (4) streptomycin, P A S and thioparamizone In this series the best results were attained using methods (3) and (4)

Lane (1951) has reported a series of 52 cases, 9 of whom received streptomycin and moogral, the remainder streptomycin and potassium iodide The latter is believed to promote solution and absorption of caseous material exposing masked tubercle bacilli to the influence of the streptomycin A 48 per cent conversion rate is claimed Streptomycin and potassium iodide is considered the most promising combination The most marked success was attained in those patients in whom the urine from the solitary remaining kidney contained tubercle bacilli, but in whom no obvious renal lesion was demonstrated This type of case has also responded well to streptomycin alone, and to streptomycin and P A S as reported above It may, however, be of some significance that the cases treated by Lane, in the above series, were not subjected to sanatorium regimen

In 11 of the 52 patients treated, calcification of the kidney was noted In only one of these was urine conversion attained, this patient reverted to positive after one year The author concludes that in the presence of calcification, even to a minimal extent, success is most unlikely

Lane has also reported the success of bladder instillations in the treatment of patients in whom tuberculous cystitis has persisted after nephrectomy The substance used is designated B 53 It is a soap derived from a branched fatty acid used in 0 5 per cent water solution buffered to *p*H 7 2 In patients with cystitis and spread to the remaining kidney, local treatment proved unsuccessful

A preliminary report on B 283 is included This drug, a phenazine dye, was given orally to 8 patients An immediate conversion rate of 50 per cent is reported, but in half of these relapse occurred, leaving a conversion rate of 25 per cent at the time of the report

In this brief communication the work performed at Robroyston Hospital has been detailed, and reference has been made to the conclusions of other workers By many the chemotherapy of renal tuberculosis may be condemned by the multiplicity and diverse combinations of drugs employed The variety of reagents subjected to investigation is, however, an index of the increasing ambition on the part of both surgeon and tuberculosis physician to solve the problem of renal tuberculosis

Chemotherapy has been shown to have positive value in the treatment of early renal tuberculosis, to offer some degree of protection to the contralateral kidney, and to improve the bladder in secondary tuberculous cystitis following nephrectomy In addition, though the incidence of post-operative dissemination in renal tuberculosis is low, it is significant that no such occurrence has been reported in patients receiving chemotherapy

It is becoming increasingly obvious that the majority of workers in this field are discarding the doctrine of immediate nephrectomy for renal tuberculosis From the time of diagnosis the patient should receive sanatorium treatment, under the supervision of a tuberculosis physician, the latter working as an integral part of a urological team

REFERENCES

JACOBS and BORTHWICK, (1950), " Streptomycin in Urinary Tuberculosis," *Proceedings of the Royal Society of Medicine* (June), Vol XLIII, No 6, pp 453-466 (section of Urology, pp 19-32)

LLOYD, F, BAUMRUCKER, G and STONINGTON, O (1948), " The Treatment of Urinary and Genital Tuberculosis with Streptomycin," *Surgical Clin N A* (December), pp 1639-42

LATTIMER, J K *et al* (1948), " Streptomycin Treatment of Genito-Urinary Tuberculosis " *Tuberculosis Journ Ur* (December), **60**, 974-85

LJUNGGREN, Communication

LANE, T J D (1951), " Chemotherapy in Urinary Tuberculosis," *Irish Journ of M S* (September), **309**, 393-405

ROSS, J C *et al* (1951), "The Bacteriostatic Effects of the Newer Drugs in the Treatment of Genito-Urinary Tuberculosis," *Lancet* (May), **1**, 1033–36

RENAL TUBERCULOSIS

ITS PATHOGENESIS AND MANAGEMENT IN PATIENTS WITH EXTRA-UROGENITAL DISEASE

By WALTER M BORTHWICK, Ch M

Robroyston Hospital, Glasgow

IN my talk this afternoon, I intend dealing with the problem of renal tuberculosis, occurring firstly, as the only obvious manifestation of tuberculosis, and secondly, as a lesion coincidental to other obvious clinical disease I do not intend, however, to make that distinction a sharp one, but I shall try to give the most recent views on the pathogenesis of renal tuberculosis and our ideas in Robroyston Hospital with regard to the management of the patient with renal and extra-urogenital tuberculosis I shall also try to show that renal tuberculosis is more common than many suspect, and I am convinced that success in a campaign against this disease rests to a great extent on the tuberculosis physician, who is often in a position to initiate the investigation and diagnose the condition in its pre-clinical stage at a time when chemotherapy is likely to be most beneficial As in all forms of tuberculosis, the sanatorium regimen is still the mainstay in treatment, and any tendency to dissociate the tuberculous patient from a sanatorium or a tuberculosis hospital for any part of his treatment, I feel, is a retrograde step

For some statistical details on renal tuberculosis I have abstracted the case records of the last 200 patients in Robroyston Hospital suffering from that disease These patients have all been in hospital within the last three years, but the time element is of no importance since no follow-up will be given

TABLE I

Age Incidence in 200 *Patients with Renal Tuberculosis*

Age in Years	—10	—15	—20	—25	—30	—35	—40	—45	—50	—55
Number (Females)	1	4	12	23	14	10	5	2	3	1
Number (Males)	3	5	22	23	33	16	14	3	2	4
Total	4	9	34	46	47	26	19	5	5	5

Females, 75 Males, 125

Read at a meeting of the Tuberculosis Society of Scotland held at Bangour Hospital on 25th January 1952

The age incidence can be seen from Tables I and II The incidence in females seems to be higher than in males in the earlier age groups, but in both sexes over 85 per cent of the cases occurred between 16 and 40 years of age The higher incidence in males has been a constant feature since a definite genito-urinary unit was established in Robroyston Hospital in 1934 and up to date the reason for this has eluded us I shall be grateful for any suggestions on this finding

TABLE II

Percentage Incidence in 200 *Patients*

Age in Years	16–25	16–30	16–35	16–40
Female	46 7	65 3	78 7	85 3
Male	36	62 4	75 2	86 4
Total	40	63 5	76 5	86

TABLE III

Incidence of Extra Genito-Urinary Tuberculous Lesions (200 *Patients*)

Total	Number with other Lesions	Per Cent
125 (Males)	52	41 6
75 (Females)	36	48
Combined Males and Females	88	44

TABLE IV

Localisation of Extra Genito-Urinary Lesions

Site	Males	Females	Total
Lungs	23	6	29
Lungs and Bone	8	3	11
Lungs and Joint	5	5	10
Glands	0	5	5
Bone	10	11	21
Joint	5	5	10
Multiple	1	1	2

The incidence of clinical extra-urogenital disease in these patients was 44 per cent (Table III), and the localisation of these lesions can be seen in Table IV

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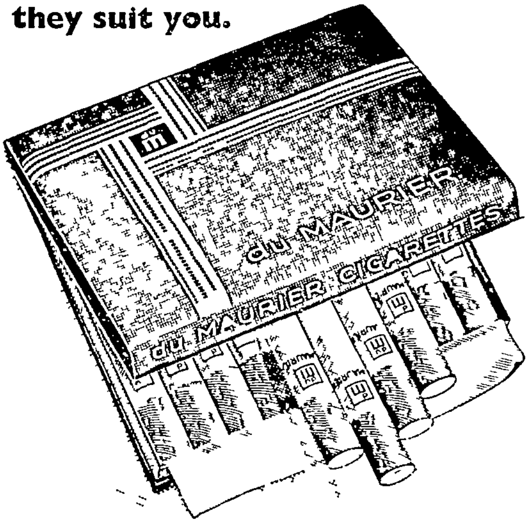

CORK TIP IN THE RED BOX—PLAIN TIP (MEDIUM) IN THE BLUE BOX

I tried to find out the sequence of events in the tuberculosis history of the 88 patients who had extra-urogenital disease, but accurate details were only possible in 64 instances (Table V) As far as could be ascertained the renal lesion was diagnosed from one to over ten years after the other tuberculosis manifestations

TABLE V

Interval (in Years) between Extra-Urogenital Lesions and Diagnosis of Renal Tuberculosis (64 *Patients*)

Time in Years	1	2	3	4	5	6–10	10+
Number	11	10	12	6	4	15	6

An obvious difficulty here is my lack of follow-up to see how many of the 200 patients will develop lung or bone and joint disease It is, however, a very definite impression that the number of patients with renal tuberculosis who subsequently develop a pulmonary or bone lesion is very small I shall try to give a possible explanation of this later

The presenting symptom which initiated the urological investigation in these 200 patients (Table VI), was an increased frequency of micturition in 97 or just under half, pain in 9 (4 5 per cent), hæmaturia in 22 (11 per cent), and retention of urine in 4 (2 per cent) In the remaining 68 patients there was none of the generally recognised symptoms of renal tuberculosis, and the investigation was carried out after routine examination had shown tubercle bacilli in the urine or an unexplained pyuria or albuminuria (Table VII)

TABLE VI

Signal Symptom, if any, Causing Urological Investigation in 200 *Cases of Renal Tuberculosis*

Symptom	Increased Frequency of Micturition	Pain	Hæmaturia	Retention of Urine	None
Number	97	9	22	4	68

TABLE VII

Reason for Urological Investigation in 68 *Symptom Free Patients*

	Tubercle Bacilli in Urine	Albuminuria	Pyuria	Epididymitis
Females	10	5	2	
Males	5	1	1	44

Many of you know our ideas on the subject of genital disease in the male, and it is routine procedure to carry out a full urological investigation in these men Forty-four of the 68 patients suffered from tuberculous epididymitis without any urinary upset, and one can almost say like Wells (1943), that epididymitis can be included in the symptomatology of renal tuberculosis in the male That a very close association exists between renal and genital disease in the male is clearly demonstrated in Table VIII Over 80 per cent of the 125 men had genital disease, 66 4 per cent having combined epididymal and pelvic genital disease and 15 2 per cent having pelvic involvement alone I have no doubt that follow-up of the 19 men will show subsequent epididymitis in many of them

TABLE VIII

Incidence of Genital Tuberculosis in 125 Males Suffering from Renal Tuberculosis

	Number	Per Cent
Combined Epididymal and Pelvic Genital Disease	83	66 4
Pelvic Genital Disease alone	19	15 2
Total	102	81 6

The localisation of the kidney disease when first diagnosed (Table IX), was unilateral in 154 and bilateral in 46 The frequency of involvement of right and left kidney was the same In these cases with bilateral involvement the disease was definite and sometimes advanced in 34, while the remaining 12 had tubercle bacilli in both kidney specimens but no disease was demonstrable in the urograms With regard to the 68 symptom-free patients, the disease was bilateral in 18 instances, in 7 of which moderate to advanced lesions were found Eleven patients in this group had tubercle bacilluria Medlar (1926, 1932) and Band (1935, 1943) have proved that the isolation of tubercle bacilli from the kidney urine means that there is a renal lesion

TABLE IX

Localisation of Kidney Disease —
Right Kidney—77
Left Kidney—77
Both Kidneys—46 (12 excretory bacilluria)

Localisation of Kidney Disease in 68 *Symptom free Patients* —
Right Kidney—23
Left Kidney—27
Both Kidneys—18 (11 excretory bacilluria)

From the above findings a point worthy of stress and not always realised, is that renal tuberculosis may be bilateral and advanced without any urinary symptoms In point of fact the only true symptoms of renal tuberculosis are hæmaturia arising from the kidney and very occasionally renal pain The commonest symptom, as quoted, increased frequency of micturition, is not really a symptom of renal tuberculosis but a symptom of vesical disease, and that may develop soon after the start of open renal tuberculosis some years later or not at all Most textbooks on this subject stress the general symptoms with which one associates an early tuberculous lesion elsewhere in the body The loss of weight, appetite and lassitude and other symptoms of tuberculous toxæmia are all given an important place in the diagnosis of renal tuberculosis In our experience, these signs and symptoms occur as the exception rather than the rule in patients who do not have any extra-urogenital tuberculous disease Toxæmia from a renal lesion seems to be minimal, and I would be interested to hear any observations on the reason for this When the bladder becomes involved then the increasing frequency of micturition during the day and night has its effect on the general well-being of the individual Even when epididymitis develops, apart from the initial upset lasting days rather than weeks or months, the patient usually shows little evidence of toxæmia It has long been recognised in Robroyston Hospital that the patients who are under treatment for renal tuberculosis without any other tuberculous disease are by far, apparently, the healthiest patients in the hospital Even in progressive renal disease, in the absence of very marked vesical irritability, that well-being may continue until most of the renal tissue is destroyed and the patient approaches a uræmic condition Weight, blood sedimentation, appetite, blood urea and general examination may all remain normal until a short time before the onset of uræmia One obvious exception to this is the pyonephrotic kidney, which produces a marked reaction in all these tests in the individual

To sum up this section, I would stress the importance of a full urological examination in tuberculous patients who have albuminuria or pyuria Routine examination of the urine for tubercle bacilli will produce surprising results, while epididymitis demands a full examination Hæmaturia, renal pain or increasing frequency of micturition are all well recognised as symptoms necessitating a urological investigation

Since Medlar (1926, 1932) demonstrated by serial section that bilateral tuberculosis of a microscopic nature could be seen in the kidneys of many patients who had died of extra-urogenital tuberculosis, our conception of the origin of renal tuberculosis has developed The primary complex in tuberculosis is usually in the lungs or intestines, and later that may be followed by a bacillæmia in which the organisms are carried to various parts of the body Thereafter there is a latent period depending on the number and virulence of the organisms and the resistance of the host According to Wallgren, quoted by Ljunggren (1951), if the infection develops near the serous membranes it usually manifests early, and later if the bones and joints are affected The kidney lesions develop still later The earliest lesions in the kidney are usually bilateral and found in relation to the glomeruli of the cortex, constituting the sub-clinical phase These lesions may heal or become encysted If the former occurs it could account for a later unilateral or " surgical kidney," but if the latter happens, at any time reactivation due to re-infection may occur As stated by Ljunggren, the cortical lesions may ulcerate into the renal tubules and give rise to tubercle bacilluria At this stage pyuria may be absent or slight and urography will demonstrate normal function and outline The cortical foci may spread directly or by lymphatics to the tubules of the pyramids and give rise to a definite lesion The blood supply of the pyramid, especially in the papilla, is poorer than in the cortex, and the chances of healing are not so favourable Healing foci in the papilla are rare, and instead there is a tendency to necrosis and cavity formation When this has ulcerated into the renal pelvis, the infection can spread to the ureter, bladder, and in the male to the genitalia

At this stage (Band, 1948), the renal pelvis has now become infected, and tubercles and ulceration occur in the lining membrane Renal function is impaired and the renal pelvis becomes atonic Residual urine which is present becomes reabsorbed, and tubercle bacilli pass in a retrograde manner to the tubular systems of the neighbouring calyces Secondary foci then appear as confluent groups of tubercles in more distant zones of the renal cortex This condition is often seen after nephrectomy, when the kidney, on section, may show cavitation in relation to the upper group of calyces and numerous tubercles in the cortex near the lower pole

The hæmatogenous dissemination of tubercle bacilli is not limited to the kidneys, since renal tuberculosis and bone and joint lesions are frequently associated Irrespective of the time of onset of these lesions, and I personally believe that the orthopædic lesion usually manifests itself earlier in the majority of cases, one must accept the fact that miliary tuberculosis is much more common than most of us realise We must regard miliary tuberculosis as a quantitative rather than a qualitative conception, since it follows that miliary tuberculosis not only occurs frequently but that in most cases it is relatively innocent in character Apart from the possibility that clinical miliary tuberculosis may arise, there is the alternative that pre-clinical miliary tuberculosis is either cured or that it passes into chronic tuberculosis of the organs such as kidneys or bone and joint

Another thought at this stage from the point of view of prognosis is, that whatever treatment is considered for unilateral renal disease, and nephrectomy is usually the method of choice, it must be remembered that the contralateral kidney nearly always has at least a minute lesion which may break down Therein, I feel, lies a possibility for chemotherapy

It is important to realise that the term renal tuberculosis has largely been superseded by the more accurate ones of genito-urinary or urogenital tuberculosis These names recognise that we are dealing with a system-disease in which the kidney is usually the primary source, showing a great tendency to spread to other organs in the same system The resulting lesions often show a varied character in the different organs There can be small renal lesions with marked vesical disease There can be extensive bilateral renal tuberculosis without cystitis This varied response may also be evident in that nephrectomy for unilateral renal disease is sometimes followed by healing of vesical disease, while in others aggravation of the vesical condition occurs It is not infrequent to find in men with progressive and not long-standing genital disease, calcified lesions in the kidney or even calcification of the whole kidney Presumably the genital disease in most has been caused by a spread from the kidney, yet the stages of infection and response of the various organs has been so different Removal of the kidney does not influence genital disease

When renal tuberculosis is diagnosed in its symptom-free phase it does not always mean that it is diagnosed at an early phase Generally the disease is slowly progressive, so slow sometimes that many years may pass without obvious change in the affected individual That does not mean, however, that we can consider renal tuberculosis as a chronic, unimportant event in a tuberculosis case history This disease is a fatal one requiring sanatorium treatment when diagnosed, but the chronicity becomes important when the patient also suffers from extra-urogenital tuberculosis Close liasion between the surgeon and tuberculosis specialist is of highest importance in these cases and, if necessary, the deciding vote as to the general conduct of the case should lie with the tuberculosis physician

In Robroyston Hospital, beds are set aside for patients with renal tuberculosis, and on an average 40 to 50 patients are usually in residence at any one time The 200 patients about whom I spoke earlier were all in hospital within the last three years, some in fact being still there When possible, the unit consists of two sections, one male and the other female, situated in wards containing non-pulmonary tuberculous patients The presence of open pulmonary tuberculosis excludes the patient from the unit, and accommodation is found in a pulmonary ward

It is difficult to particularise with regard to our ideas on the management of the patient with multiple tuberculous lesions In general, I feel that progressive pulmonary or active bone or joint disease should have preference over active intervention in renal tuberculosis The watchword should not be early nephrectomy but nephrectomy during the most suitable period when other lesions are at least under control Chemotherapy has changed our ideas a little, and that will be discussed later, but even with chemotherapy it is advisable to control the extra-urogenital lesions before embarking on operative intervention There are exceptions, one of which I have mentioned before The pyonephrotic kidney, even in the presence of progressive pulmonary disease, should be removed as early as possible A frequency of micturition which disturbs the patient day and night to such an extent that the general condition suffers, should, if possible, receive treatment

Disease of the smaller joints does not, as a rule, interfere with the management of a case The larger joints, especially the hip, should, if possible, receive prior claim, since instrumental investigation and operative intervention may have a deleterious effect Spinal tuberculosis also, should be in a quiescent phase, since theoretically the position at operation may cause damage, although in the more urgent operations on the urinary tract I have never recognised any such damage

With regard to pulmonary tuberculosis, events can move with such rapidity and with such disastrous results that control of this disease should always be attempted before urological interference is undertaken Close observation of the renal tract can be carried out without serious upset to a patient with active pulmonary disease If instrumental investigation is considered inadvisable, and that is seldom, then rarely does intravenous urography do any harm

I do not wish to give the impression that renal tuberculosis can be considered as an unimportant incident The advanced stages of this condition cause probably more upset and discomfort than a similar period in almost any other tuberculous lesion A frequency of micturition at five-, ten- or fifteen-minute intervals obviously makes life intolerable and everything possible should be done to prevent this or treat it The point I would like to make is that in a patient with pulmonary and renal tuberculosis, when both conditions are suitable for treatment, then in my opinion, the pulmonary disease should receive prior claim, always provided that close watch is kept on the genito-urinary condition. It is only advisable to avoid nephrectomy until the lung lesion is under satisfactory control, not to wait until so-called healing has taken place. In the individual with untreatable pulmonary tuberculosis, then all necessary steps should be taken to treat coincidental renal disease to avoid undue suffering from bladder irritability

Each case of urogenital tuberculosis should be under the supervision of the tuberculosis specialist in a sanatorium or tuberculosis hospital, and close liasion with the surgeon should exist so that the latter can carry out in the words of Cibert (1946) not " la néphrectomie précoce " but " la néphrectomie opportune "

REFERENCES

BAND, D (1935), *Edin Med Journ* , 42, 162

BAND, D (1943), *Post Grad Med Journ* , 19, 266

BAND, D (1948), *Textbook of Genito-Urinary Surgery,* ed by H P Winsbury-White, Edinburgh

CIBERT, J (1946), *La Tuberculose Renale,* Paris

LJUNGGREN, E (1951), Personal Communication

MEDLAR, E M (1926), *Amer Journ Path* , 2, 401

MEDLAR, E M (1932), *Urol and Cut Rev* , 36, 71

WELLS, C A (1943), *Post Grad Med Journ* , 19, No 217, p 270

SOME UNUSUAL MANIFESTATIONS OF ABORTUS FEVER

By A W BRANWOOD, M D, F R C P E, M R C P

MANY physicians are of the opinion that abortus fever is rare in this country It is very seldom diagnosed, although some workers are convinced that many cases of this disease exist and produce chronic ill health in the community

Sir W Dalrymple-Champneys, in his Milroy Lecture of 1950, stated that undulant fever is a neglected problem in this country He quoted only 983 cases in England and Wales during the past twenty years Other authors have similar figures There were no proved cases of abortus fever admitted to the Edinburgh Royal Infirmary from 1932-1936 and only occasional cases thereafter

Dalrymple-Champneys has explained the small number of cases of brucellosis in this country as being due to (1) a general impression that abortus fever is a rare disease, (2) the diagnosis of abortus fever is too readily excluded by one negative agglutination, (3) the low mortality of this disease has not brought it to the public eye

Another explanation is that abortus fever may mimic many other conditions and its mode of onset can be so unusual that the diagnosis of undulant fever may never be considered

During the years 1942-1952 the author has seen 10 proved cases of brucellosis In only 3 of these could the disease be described as typical The majority of cases had a most unusual onset and the diagnosis was only made later Once the diagnosis had been made, however, these cases could be divided into the ambulant, undulant, continuous or malignant groups, again illustrating the fact that a diagnosis of brucellosis can usually be made once one thinks of it

CASE MATERIAL

The cases seen by the author occurred in Cheshire and in the Royal Infirmary, Edinburgh In 7 of these cases it was the mode of onset which was misleading They presented as (1) Meningitis, (2) Appendicitis, (3) Anæmia and Splenomegaly, (4) Pleurisy, (5) Hepatitis, (6) Rheumatism, (7) Gastro-enteritis

(1) *Meningitis* —A veterinary surgeon aged 26 was admitted to hospital suffering from generalised aches and pains for about a fortnight On the day of his admission he suddenly became drowsy and complained of intense frontal and occipital headache He had neck rigidity and presented a typical picture of meningeal irritation He had a furred tongue and sweated profusely His temperature was 102° and he had tachycardia The W B C was 6200 with an absolute lymphocytosis He was not anæmic Lumbar puncture

yielded clear cerebro-spinal fluid under reduced pressure with a slightly increased protein content and 16 lymphocytes per c mm A provisional diagnosis of benign lymphocytic chorio meningitis or early T B meningitis was made In view of the patient's occupation, however, an agglutination test for *B abortus* was performed This was negative in dilutions of 1 16 upwards The patient was treated with analgesics for his headache He remained drowsy for two or three days during which time he ran an intermittent fever of 101°-102° F and then suddenly became afebrile, looked much better and stated that he now felt fit A week later the patient was still afebrile but his spleen was now slightly enlarged Another agglutination test for *B abortus* gave a positive agglutination of 1 256 upwards

The patient admitted that recently he had been working in a bacteriology department making a vaccine for abortus fever, but as far as he knew had not inoculated himself

(2) *Acute Appendicitis*—A farm worker aged 21 was admitted to hospital with symptoms of acute appendicitis A laparotomy was performed and the appendix which appeared healthy was removed Subsequent histological examination showed the appendix to be normal Four days after his operation the patient developed flitting pains in all his joints and a severe pain in his left shoulder The transient joint pains abated but the pain in the shoulder persisted The patient had a low grade pyrexia of 100°-101° F and profuse night sweats His white blood count was 6000 with 55 per cent lymphocytes The B S R was 22 mm per hour Agglutination for *B abortus* was negative in dilutions of 1 16 upwards The patient was given full doses of salicylates and his temperature became normal His left shoulder was still painful and there were still night sweats X-ray of the chest showed no evidence of pulmonary tuberculosis At this time the spleen became palpably enlarged In view of the symptoms and signs a provisional diagnosis of undulant fever was made in spite of a negative agglutination test The patient was given aureomycin and the profuse night sweats stopped in two days The shoulder became less painful and the patient looked and felt better He was discharged a fortnight later, the agglutination reaction for *B abortus* being still negative He was seen again in 6 weeks' time He had kept perfectly fit during this period The serum now showed agglutination to *B abortus* up to 1/512

Although this patient was a farm worker he stated that as far as he knew no cattle on the farm were diseased nor had there been any "spontaneous abortion" among the herd

(3) *Anæmia and Splenomegaly*—A girl of 12 was admitted to hospital with a complaint of frontal headache, intermittent epistaxis and sore throat of a few days' duration She stated that for several weeks prior to this she had felt weak, easily tired, breathless on exertion and had sweated profusely at night On examination she looked pale and tired and far from healthy and had a nocturnal pyrexia of 101°-102° Her spleen was palpable The blood picture was as follows —Hæmoglobin 70 per cent, R B C 4,000,000, C I 0 87, W B C 4200 with 54 per cent small lymphocytes, 40 per cent polymorphs, 6 per cent monocytes and 2 per cent eosinophils Sternal puncture showed a normoblastic marrow An X-ray of the chest was normal and the Widal reaction and a blood culture were negative A provisional diagnosis of a reticulosis, perhaps Hodgkin's disease, was made and the patient was treated symptomatically At weekly intervals blood cultures, Widal and Paul Bunnell reactions and agglutination for *B abortus* were performed For

three successive weeks these were all negative During this time the patient gradually improved—the sweating became less, the temperature returned to normal and she looked and felt much better There was an increase in her weight and her hæmoglobin was now 88 per cent There was still a leucopenia, however, and the lymphocytes remained above 55 per cent of the total W B C The liver and spleen were smaller although still palpable At the end of a month the agglutination tests were again repeated and on this occasion the serum agglutinated *B abortus* up to dilutions of 1/512 and a week later agglutination of *B abortus* was obtained in dilutions of 1/1024

The patient was seen again 3 months later She was very fit and not anæmic The spleen was no longer palpable The white blood count was 6000 per c mm but with still 40 per cent lymphocytes The serum still agglutinated *B abortus* in dilutions of 1/1024

This girl lived in the country and told us she drank a lot of milk

(4) *Jaundice*—A man of 23 had complained of anorexia, general malaise and attacks of shivering for a week This was followed by a frontal headache and the gradual onset of jaundice On examination this young man had mild jaundice, a very furred tongue and a soft tender liver which was enlarged to two finger breadths below the costal margin The spleen was enlarged to percussion The stools were pale and the urine contained bile and urobilinogen The temperature varied between 97° F and 100° F The white blood count was 4600 with 48 per cent lymphocytes A cephalin cholesterol flocculation test showed [++] (2) The patient was thought to be suffering from infective hepatitis and was treated accordingly After about 14 days the jaundice had disappeared, there was no bile in the urine although there was still urobilinogen, and the liver was just palpable The cephalin cholesterol was [+] (1) The spleen was now definitely palpable In spite of the disappearance of the jaundice the patient, contrary to expectation, felt no better His tongue was heavily coated He developed profuse night sweats and the temperature persisted There was still a leucopenia and a lymphocytosis A Widal reaction was negative but the serum agglutinated *B abortus* in dilutions up to 1/512, and 4 days later the serum gave a positive agglutination to *B abortus* up to 1/1024

This man was a town dweller and there appeared to be no obvious source of infection in this case

(5) *Rheumatic Fever*—Undulant fever may often cause arthritis and in some instances it can be mistaken for rheumatic fever, as is seen in the following case

A man of 46 years, a dockyard worker, had suffered from a mild attack of "influenza" three weeks previously He apparently recovered from this and then, ten days later, suddenly complained of severe pains in all his joints This symptom was accompanied by profuse sweating and a temperature of 101° F He had a tachycardia and was diagnosed as a case of acute rheumatism The joint pains did not improve when the patient was given massive doses of salicylates, indeed the man appeared worse His temperature varied between 97° and 100° F The sweating persisted, especially at night The white blood count was 4800 with 57 per cent of lymphocytes The B S R was only 32 mm per hour His spleen, not palpable on admission, became enlarged three days later Undulant fever was suspected and the serum agglutinated *B abortus* in dilutions up to 1/256

This man could give no explanation as to how he might have acquired the disease although he had been helping to unload a cattle boat four weeks previously

(6) *Pleurisy and Pericarditis*—A girl of 18 years, previously healthy, suddenly developed severe substernal pain which radiated into the neck She was admitted to hospital On admission the temperature was 102° F, her B S R was 97 mm per hour and there was a tachycardia of 102 per minute Pericardial friction was audible over the whole of the præcordium The patient was diagnosed as a case of acute rheumatic pericarditis and was given massive doses of salicylates Her tachycardia persisted and the temperature fell to 99° F The friction rub persisted Five days later the temperature suddenly rose to 104° F and she complained of pains in most of the larger joints The white blood count at this time was only 3200 with 50 per cent lymphocytes The pericarditis remained and there was now a left-sided pleurisy The temperature became hectic, swinging from 97° F to 105° F The patient was desperately ill and sweated profusely Her blood culture and all agglutination tests, including *B abortus*, were negative Penicillin was administered purely empirically with absolutely no effect The patient developed a small left-sided pleural effusion The aspirated fluid was serous and sterile She was given streptomycin with no improvement At the end of a fortnight the temperature fell and remained normal The pericarditis and pleurisy had cleared up An electrocardiograph and X-ray of the chest were normal The white blood count was only 4000 and there was still a lymphocytosis She also had a mild hypochromic anæmia Fourteen days later she again complained of pains in the shoulder and hip joints and the temperature rose to 105° F The drenching sweats returned In three days' time everything had once again returned to normal She now had splenomegaly and agglutination for *B abortus* was positive in dilutions up to 1/256 The patient was treated with aureomycin with a very dramatic improvement

This girl although residing in a town had just returned from a holiday in the country prior to the onset of her symptoms She denied any contact with infected cattle or indeed drinking an excessive quantity of milk

(7) *Gastro-enteritis*—A man aged 63 was admitted to hospital with a history of the sudden onset of colicky abdominal pain, diarrhœa and vomiting For several days he was sick after everything he ate and the diarrhœa was very troublesome He developed a frontal headache during this period and his temperature varied between 97° F in the morning and 102° F at night He was treated symptomatically as a case of gastro-enteritis After five days he felt better and the diarrhœa had stopped although he still complained of headaches in the evening when his temperature was elevated Examination of the abdomen on admission revealed generalised tenderness which rapidly improved *pari passu* with his condition The spleen, however, then became palpable At no time was the white blood count higher than 5000 and there was a persistent lymphocytosis of 53 per cent The Widal reaction was negative and there was no agglutination of *B typhosus* or *B paratyphosus* A or B in serum dilutions of 1/16 upwards Bacteriological examination of the stool revealed a normal flora Three days later the agglutination tests and Widal reaction were repeated, again with negative results The patient's serum was also tested against *B abortus* and agglutination was obtained in dilutions 1/16 to 1/512 Twelve days later agglutination was obtained with *B abortus* in dilutions of 1/16-1/1024

Throughout this period, once the acute gastro-intestinal symptoms had spontaneously abated, the patient felt perfectly fit but still had a pyrexia at night He was treated with *B melitensis* vaccine and the temperature gradually returned to normal

This patient was a gardener and, although a countryman, stated he had not been in contact with diseased cattle nor had he drank any more milk than the rest of his family who were all well

The above cases illustrate some of the ways in which undulant fever may present It can be seen how easily some of these cases of abortus fever may be misdiagnosed and, due to a spontaneous remission, be entirely missed, only to lead to chronic ill health at a later date It cannot be too strongly emphasised that brucellosis must always be kept in mind in the differential diagnosis of many conditions

There are several points about brucellosis that are well worth consideration

(1) *Ætiology*

Evans and other workers, including Fitch and Dubois, have shown that the disease can be transmitted to humans by goats, sheep, swine, cats, dogs and horses The recognised source of infection in Britain, however, seems to be mostly bovine, although horses suffering from fistulous withers may transmit the disease to humans Individuals become infected by drinking raw milk or eating milk products from the milk of infected cattle

It is very unlikely that butter and cheese transmit the infection, for the lactic acid of the sour milk is bacteriocidal for the brucella organisms Butter and cheese, however, if freshly made, may contain a few organisms and thus act as a source of infection

Direct contact with infected animals or their carcases or excreta may also provide a route of infection Garrod has demonstrated that of all the intestinal pathogens, brucella is the most susceptible to the acid gastric juice It is often stated that a period of ill health or some short acute illness, where there may be a temporary associated achlorhydria, precedes the initial attack of undulant fever In only one patient in this series, the man diagnosed initially as rheumatic fever, was there any history of some previous ill health before the onset of his symptoms It is suggested therefore that people in good health do not become infected by the brucella abortus

In only one patient in this series, the veterinary surgeon, was there any possibility of tracing the infection There was a possibility of contact infection in the dock worker who had recently helped to unload a cattle boat One of the other patients worked on a farm, and three more were country dwellers, but no history of any mode of infection was present in these cases other than the possibility of drinking raw milk

These few cases illustrate very well one of the features of this disease, namely, its sporadic occurrence and, in many cases, complete absence of any apparent source of infection

(2) *Sex Incidence*

Many workers have stressed the difference in sex incidence of this disease Brucellosis is far more commonly seen in men than in women This may be occupational, although other factors seem to play a part in determining this sex incidence In this series there were 5 men and 2 women The ages of the men varied from 18 to 65 years The two females were aged 12 and 18 Magoffin *et al* in their series of abortus fever found that 78 per cent were males, but stated that in the age groups under 13 and over 35 the sex incidence was approximately the same Olin and Taylor had similar results, and the latter suggested that females after puberty seem to be relatively immune to abortus fever or at least to clinical attacks of this disease This apparent immunity may disappear after the menopause, for the incidence of the brucellosis is the same in both sexes over the age of 65 years

CLINICAL MANIFESTATIONS

Undulant fever usually has an insidious onset In the majority of patients the symptoms are increasing tiredness, lethargy, occasional headaches and sweating It is when the onset is sudden and dramatic that the condition is so often missed, for in these cases the disease may mimic practically anything Dalrymple-Champneys has stated that when the onset is sudden the presenting symptoms may resemble a variety of conditions from pneumonia to melæna

The very few cases in this series show how diverse are the clinical features of abortus fever and how sudden the onset may be

Most authors have classified the disease into the five well-known types, namely, the ambulant or mild, the undulant or ordinary type, the intermittent, continuous and the malignant variety Yet because the onset may be sudden and the condition at first undiagnosed it is sometimes difficult to fit the disease into one of these five types

Sweating is the most frequent and severe symptom In these cases drenching sweats were a marked feature of every one This sweating, however, may be only mild or moderate Nevertheless, be this symptom mild or severe it always occurs in the late afternoon or at night and is accompanied by a very characteristic sour smell which should be almost diagnostic of the undulant fever

Tiredness and lethargy are complained of bitterly during the height of the fever, only to disappear when the temperature is normal This state of well-being, insisted on by the patients during their apyrexial periods, is again almost pathognomonic of brucellosis

Headache is a noticeable feature In some instances it can be so severe that the condition is mistaken for meningitis, as in the case in this series Hughes in 1897 mentions a patient who, having been ill for several weeks, developed symptoms of cerebral irritation, and at post mortem *B melitensis* was isolated from the meninges Lemaire studied several non-fatal cases of brucella meningitis and pointed out the similarity of meningitis due to brucellosis and tuberculous meningitis Thereafter other workers, including Desage, Magnani and Roger, described similar cases and stressed the difficulty of diagnosis between tuberculous and brucella meningitis

Pain is another common complaint It is usually situated in the joints In most cases only one or two joints may be involved In some patients, however, the disease can begin suddenly as in the man in this series, with acute polyarthritis and may easily be mistaken for rheumatic fever The pain may also be present in the muscles, especially of the back or the abdomen In the latter case the sudden onset of abdominal pain leads to a mistaken diagnosis of acute appendicitis in many patients

Respiratory symptoms are also encountered These may vary from the symptoms of bronchitis to those of an acute pneumonia Pleurisy was present in one girl in this series

Cardiac Manifestations

Rennie and Young in 1936 first described endocarditis due to a brucella in this country, and Hardy *et al* reported similar cases in the American literature Since then other cases have been recorded in Scandinavia, America and Great Britain One patient in this series suffered from both pleurisy and pericarditis Pericarditis has been described by Dalrymple-Champneys in one case of undulant fever

Splenomegaly —This sign is invariably present at some time in every case of brucellosis Indeed it is one of the most important diagnostic features of this condition

Hepatomegaly —Enlargement of the liver is not so commonly present as splenomegaly In some cases the liver may be slightly tender and, rarely, the presence of jaundice may lead to a mistaken diagnosis of infective hepatitis This happened in one patient in this series

Anorexia, constipation and diarrhœa are symptoms encountered frequently during the course or onset of the disease If diarrhœa occurs at the onset the patient may be treated symptomatically for gastro-enteritis and again the condition can be missed

Rigors are said to be a frequent feature of abortus fever The only patient with this manifestation was the girl with pleurisy and pericarditis Malaise with slight shivering, however, were early symptoms in many of the other patients

Various *skin manifestations* have been described in undulant fever, but they are neither characteristic nor specific for this condition

General Ill Health —Many American and Canadian authors have described a condition of chronic brucellosis Griggs and Scarlett maintain that in the United States and Canada chronic ill health previously explained by "rheumatism," septic foci or even neurosis are really due to brucellosis These patients have no acute episodes and show no positive agglutination tests These workers state that although brucella infection cannot be proved at the time, a positive agglutination is found years later

General fatigue accompanied by neurosis or even psychosis due to abortus infection are encountered in this country Hausmann and Schenken described a melitensis meningo-encephalitis in a patient who had been ill for a year with general fatigue, headaches, attacks of delirium and subjective sensory phenomena The infective organism was the porcine variety of brucella

Depression and apathy, an important feature of brucellosis, may be due to the long-continued fever with its periods of remission and inevitable relapses or may perhaps be explained by organic changes in the central nervous system

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of brucellosis covers so wide a field in medicine—for the disease may resemble practically any condition from P U O to depressive psychosis—that it will not be considered further It cannot be stressed enough, however, that in any disease where the symptoms are prolonged and the clinical features perhaps a little unusual a brucella infection must always be considered

DIAGNOSIS

An absolute diagnosis is often difficult to make, and in many cases is only made by surmise The diagnosis can be made by obtaining a positive culture, a positive agglutination test and, as stated by many workers somewhat ironically, a " typical " clinical picture

(a) *A Positive Culture*—This diagnostic procedure is not often performed in this country During life a positive culture may be obtained from blood, urine, fæces, sternal marrow, tonsillar swab or vagina If a suitable medium is used and the atmosphere contains an increased content of carbon dioxide, then with repeated subcultures organisms can be grown McCullough states that daily blood cultures for 7-10 days will yield a positive result in patients in whom the disease is suspected Cultures can also be obtained post mortem from the spleen, bile and lymph glands

(b) *Agglutination*—A negative agglutination does not rule out a diagnosis of brucellosis The test should be repeated frequently and a positive result may be obtained when the acute phase of the disease is over and the patient is in a remission In some cases the agglutination is persistently negative and may only become positive years later Furthermore, the test can only be a true criterion if the antigen used is satisfactory Prozones may be present and thus give a false negative agglutination Positive agglutination of sera in a dilution of 1 256 and a rising titre thereafter is proof of the diagnosis

(c) *A " Typical Clinical Picture "*—The least said about this the better Whatever the clinical manifestations, however, the blood picture in brucellosis is invariably the same There is always a lymphocytosis This can be either absolute or relative Dalrymple-Champneys has suggested that the degree of lymphocytosis bears a relationship to the agglutination titre of the patient's blood An absolute lymphocytosis is usually found when the serum is agglutinated in dilutions of 1 1000 or more Certainly a persistent lymphocytosis is a constant finding in this condition and indeed should suggest the diagnosis

SUMMARY

Several cases of abortus fever are described to illustrate the many and unusual ways in which this disease can present It is suggested that a large number of cases are missed, often being mistaken for other conditions The incidence of brucellosis in the community is thus higher than is realised Indeed many workers through the ages have stated this fact Hippocrates in 278 B C described a prolonged fever with sweating and tendencies to relapse as " the abortus epidemicus " Wilson, in 1932, suggested that if the reduction factor obtained by the relative frequency of agglutination of the typhoid group and *B abortus* by sera submitted for Widal reaction be applied to the annual notifications of typhoid fever this would give an approximate idea of the incidence of *B abortus* infection On the above basis the incidence of brucellosis would be about 400-500 per annum

Although the ætiology of this condition is well known it is difficult, in the majority of patients, to trace the source of infection or indeed explain the sporadic incidence of the disease It is suggested that a period of ill health or debility may predispose to the infection

Brucellosis must always be considered in any disease with prolonged fever or where the clinical manifestations are somewhat unusual

The advent of aureomycin offers a permanent cure to the majority of these patients Thus the incidence of brucellosis with its trail of chronic ill health and acute periods of relapse can be lessened provided the physician is fully aware (*a*) that abortus infection does occur in this country, (*b*) that it may mimic many other conditions, and (*c*) that the disease can be diagnosed by repeated blood cultures or agglutination tests

The dictum, " Was man weiss sieht man ", applies in abortus fever just as in any other condition

I wish to thank Professor Murray Lyon for the use of some of this case material

REFERENCES

DALRYMPLE CHAMPNEYS, Sir W (1950), *Lancet*, 1, 429

DESAGE, PELLERIN et VINERTA (1926), *Bull et mém Soc méd d'hôp de Paris*, 50, 872

DUBOIS, C (1911), *Rev Vet*, 3, 129

EVANS, A C (1927), *Journ Amer Med Assoc*, **88**, 630

FITCH, C P, BISHOP, L, and BOYD, W I (1932), *Journ Amer Vet Med Assoc*, **80**, 69

GARROD, L P (1937), *Journ Path and Bact*, **45**, 473

GARROD, L P (1939), *St Barts Hosp Rep*, **72**, 145

GRIGGS, J F (1943), *Calif Med*, **58**, 118

GRIGGS, J F (1948), *Journ Amer Med Assoc*, **136**, 911

GRIGGS, J F (1942), *Northwest Med*, **41**, 389

HARDY, A V, JORDAN, C F, BOOTS, I H, HARDY, G C (1930), *Nat Inst Health Bull*, No 158

HAUSMANN, G H, and SCHENKEN, J R (1932), *Amer Journ, Path*, **8**, 435

HIPPOCRATES (1849), Sydenham Society, *Hippocratic Epidemics*, Vol I

HUGHES, M L (1897), *Mediterranean, Malta or Undulant Fever*, McMillan & Co, London, p 125

Journ Amer Med Assoc, Editorial (1947), **134**, 876

LEMAIRE, M G (1924), *Bull et mem Soc, méd d'hôp de Paris*, **48**, 1636

MCCULLOUGH, N B (1949), *Amer Journ Pub Health*, **39**, 866

MAGNANI, G (1925), *Studium Napoli*, **15**, 341

MAGOFFIN, R L, KABLER, P, SPINK, W W, FLEMING, D (1949), *Amer Journ Pub Health*, **39**, 1021

OLIN, G (1935), *Acta Soc Med Suecanae*, **61**, 57

RENNIE, J K, and YOUNG, C J (1936), *Brit Med Journ*, **1**, 412

ROGER, H (1929), *Journ Méd franc*, **18**, 163

ROGER, H (1929), *Marseille Méd*, **2**, 591

SCARLETT, E P (1948), *Canad Med Assoc Journ*, **58**, 230

TAYLOR, R M, LISBONNE, M, M, VIDAL, L P, HAZEMANN, R H (1938), *Bull Health Aug L O N*, p 7

WILSON, G S (1932), *Vet Rec*, **12**, 1226

NOTES

Royal College of Surgeons of Edinburgh

At the Annual Meeting of the College, held on 22nd October 1952, the following Office-Bearers were elected for the ensuing year — *President*, Professor Walter Mercer *Vice-President*, Mr W Quarry Wood *Secretary and Treasurer*, Mr J J Mason Brown, O B E *President's Council*, Professor R C Alexander, C B E, Mr K Paterson Brown, Mr John Bruce, C B E, Mr Arthur J C Hamilton, Mr James S Jeffrey, Mr Archibald Brown Kerr, O B E, T D, Sir James R Learmonth, K C V O, C B E, Mr Robert Mailer, Dr David S Middleton, T D, Mr T McWalter Millar, Dr Douglas Miller, Mr R Leslie Stewart *Representative on the General Medical Council*, Sir Henry Wade, C M G, D S O *Conservator of Museum*, Mr James Norman Jackson Hartley, O B E *Convener of Museum Committee*, Mr John Bruce, O B E *Librarian*, Dr Douglas Guthrie

At a meeting of the Royal College of Surgeons of Edinburgh, held on 22nd October 1952, Professor Walter Mercer, President in the Chair, the following who passed the requisite examinations were admitted Fellows Amirali Abdulkarim Alidina, M B, B S UNIV BOMB 1948, Gurbux Singh Babbar M B, B S UNIV PUNJAB, 1936, Keith Loraine Barnes, M R C S ENG, L R C P LOND 1940, Alastair Kingsley Brown, M B, CH B UNIV EDIN 1941, Jitendrarao Vajendrarao Desai, M B, B S OSMANIA MED COLLEGE, INDIA, 1942 Sami Salim Khoury, M D UNIV BEIRUT, 1946, Manijah Khudabux, M B, B S UNIV BOMB 1948, Herbert Kramer, M B, B CH UNIV WITWATERSRAND 1947, Robin Campbell Wilson Lowe, M B, CH B UNIV EDIN 1945, John Donald Malloch, M B, CH B UNIV EDIN 1944, Naizby Noble, M R C S ENG, L R C P LOND 1943, Richard Douglas Oatway, M D UNIV MANITOBA, 1942, Francis Ferenc Sandor, M D UNIV BUDAPEST 1930, L R C P & S EDIN (TRIPLE) 1952, Lionel Arthur Scrivin, M B, CH B UNIV NEW ZEAL 1941, Gurmukh Singh Sekhon, M B, B S UNIV LAHORE, 1943, Shailendra Kumar Sinha, M B, B S UNIV PATNA, 1934, MS UNIV PATNA, 1944, John Robert Smith, M B, CH B UNIV GLASG 1945, David Michael Stevens, M B, B S UNIV LOND 1944, Neil Patrick Stracey, M B UNIV CALC 1946, Shelton Edgar Wijetilaka, M B, B S UNIV CEYLON, 1946

NEW BOOKS

Diary of a Psychiatrist By JAMES T FISHER, M D, and LOWELL S HAWLEY Pp 256 London Medical Publications Ltd 1952 Price 16s net

In this book Dr Fisher tells the story of his life which started with farm work, cattle ranching, and dealings in real estate Eventually, however, he became interested in Medicine and graduated at Harvard He explains that he was not interested in Surgery and thought that under such circumstances Psychiatry was the logical answer for his life work In this book he gives the fruit of his labours and experience His story is told in an interesting and sometimes in an amusing manner, but unfortunately he does not add to our psychiatric knowledge or understanding It cannot be considered a serious contribution to psychiatric literature

Portrait of a Hospital By WILLIAM BROCKBANK Pp 218, with 56 illustrations and 3 maps London Wm Heinemann 1952 Price 25s

Two hundred years have passed since the institution which was to become the Royal Infirmary of Manchester first opened its doors It was a house " with twelve beds and all other conveniences " Among the original members of the Staff was Charles White, surgeon and obstetrician, who was later to achieve world-wide fame To the original hospital no patient was admitted who " could pay for his own cure ", and a recommendation signed by a subscriber was essential At that time Manchester was a small town, but its growth was very rapid, especially during the nineteenth century The " house " was soon replaced by a new Infirmary containing 80 beds, built at a cost of slightly over £2500 Extensions and new wings were added, and in 1766 a " lunatic hospital " was built Another early requirement was met in 1779 when Public Baths were erected close to the Infirmary The Royal Patronage was accorded in 1830, and 1831 Queen Victoria paid her first visit to Manchester and inspected the building but the centenary of the great institution in the following year does not appear to have been the occasion of any celebration With the march of progress the infirmary became obsolete and even unhealthy, accordingly a scheme of reconstruction was commenced, and various improvements were made " The Great Infirmary Controversy " regarding the future dragged slowly on, and it was not until 1909 that an entirely new building was opened by King Edward VII, on a site adjacent to the old hospital which was then demolished To this magnificent new Infirmary many additions have been made, and the heavy damage caused by enemy action has been made good It is a hospital of which the city may well be proud, and the story of the 200 years of its service is well and clearly told by Dr Brockbank The book is beautifully produced the plans and illustrations are of much interest and artistic merit, and, apart from the letterpress they give a clear idea of the progress of the hospital So noble a theme deserves a good chronicle, and this book well supplies it

Surgical Gynecology By J P GREENHILL, M D Pp 350, with 101 multiple illustrations Chicago The Year Book Publishers, Inc 1952 Distributed in Britain by Interscience Publishers Ltd Price 65s (price to subscribers to the whole series of Handbooks of Operative Surgery, 60s)

Surgical Gynecology is the second volume of a planned series of Handbooks of Operative Surgery It is designed for " young gynæcologists, general surgeons and those physicians in general practice who also perform operations " After a useful section on pre-operative and post-operative care written by Dr Loeff, there follow the author's technical descriptions of operations These are illustrated, step by step, by Miss Angela Bartenbach's line drawings A few non-gynæcological operations, which it may be found necessary or desirbale to perform in the course of the gynæcologist's work, are included No attempt is made to discuss the indications for employing the procedures described, or to assess the relative merits of alternative methods of operative treatment

The descriptions so far as they go are clear, but in a few instances there is a tendency to oversimplification For example, abdominal myomectomy deserves more elaboration and the technique of dealing with a large interstitial cervical fibroid should be included Guidance in overcoming the difficulties encountered when faced with adherent pelvic masses due to inflammation or endometriosis is limited Also more help could be given in just how to define the uterine artery, how to open the ureteric canal and how to expose the obturator fossa in a radical hysterectomy Apart from plate 72, when a posterior incision mysteriously becomes located anteriorly, the illustrations are excellent and well reproduced Their number no doubt accounts for the high cost of this handbook, but this method of multiple illustration is undoubtedly the best to use when " writing up " operations

NEW EDITIONS

Synopsis of Tropical Medicine By SIR PHILIP MANSON BAHR Second Edition Pp xiii+248, with 7 plates London Cassell and Company 1952 Price 15s net

Costing the price of thirty oranges, this pocket size Synopsis answers most questions on Tropical Medicine An addition to the valuable plates records the discovery of the malaria parasite's base in the liver Space is found for Insecticides, for the revolution in the treatment of Plague, Typhus and Enteric by the use of Antibiotics, for the Sulphone treatment of Leprosy (omitting the DDS regime), for the drugs tried in seeking something better than tartar emetic in schistosomiasis, for the warning against *Stilbamidine's* toxicity

The suggestion for treating thread worms with barium meals catches the eye but one misses mepacrine amongst the anthelmintics for thread as well as for tape worms, and daraprim and acetarsol amongst the remedies for malaria and balantidiases

Scottish missionaries to Calabar will be glad to find here the modern treatment for the "eye worm"

By making marginal notes as new knowledge appears those who use this Vade-Mecum would find an easy way of keeping up to date

Principles of Human Physiology (Starling) By SIR CHARLES LOVATT EVANS, D SC, F R C P, F R S, LL D Eleventh Edition Pp xii+1210, with 709 illustrations London J & A Churchill 1952 Price 52s 6d

"Of course, like all text books, the book is patchy, superficial and out of date, patchy because it represents a menu based on my desultory reading and on current fashion superficial, when seen from the view point of research workers, in each narrow field But it does represent in summary the Principle of Physiology as I understand it" Thus with charm and conciseness Sir Charles Lovatt Evans reviews his own work in the preface Suffice it to add that the book distills the ripe experience of the best all round physiologists in Britain to day The uniform elegance of style and the integrity of outlook in this one man textbook more than compensate for inevitable weaknesses of detail The serious student of physiology (both graduate and undergraduate) will probably find this the most useful book for his shelf, both for reference purposes and to dip into at odd moments

Surgical Anatomy By C L CALLANDER Third Edition, edited by BARRY J ANSON, M A, PH D, and WALTER G MADDOCK, M S, M D, F A C S Pp xi+1074, with 929 illustrations London W B Saunders Limited 1952 Price 70s net

The need for a Third Edition of this considerable volume within nine years is evidence of its popularity in the United States As a consequence of the untimely death of the original author, the present revision has been undertaken by Anson and Maddock, the respective professors of Anatomy and Surgery in the Northwestern University Medical School of Chicago

The volume retains much of its original pattern and, as before, is beautifully produced, and lavishly illustrated by nearly a thousand drawings, diagrams, and photographs The lack of colour in the illustrations is a disadvantage, and for a text of surgical anatomy, too many of the figures are of purely pathological or surgical interest

Nevertheless, the present edition will be valuable to young surgeons and to those studying for the higher surgical diplomas, to whom the innumerable and well illustrated operative techniques will undoubtedly be educative

BOOKS RECEIVED

ANDERSON, W A D, M A, M D, F A C P Synopsis of Pathology Third Edition (*Henry Kimpton, London*)	60s net
BONNEY, VICTOR, M S, M D, B SC (LOND), F R C S (ENG), HON F R A C S, HON F R C O G, M R C P (LOND) A Textbook of Gynæcological Surgery (*Cassell & Co Ltd*)	60s
BROMPTON HOSPITAL REPORTS (*Gale & Polden Limited, Aldershot*)	12s 6d net
Edited by BROWNE, O'DONEL, M B, M A O, M A, LITT D, F R C P I, F R C O G The Rotunda Text book of Midwifery for Nurses (*John Wright & Sons Ltd, Bristol*)	21s Postage 5d
CHAMBERLAIN, E NOBLE, M D, M SC, F R C P Symptoms and Signs in Clinical Medicine Fifth Edition (*John Wright & Sons Ltd, Bristol*)	55s Post 1s 1d
CRUIKSHANK, ALISTAIR G, F R C P The Pocket Prescriber and Guide to Prescription Writing Fifteenth Edition (*E & S Livingstone Ltd, Edinburgh*)	5s net Postage 3d home
Editor in Chief, CORCORAN, A C Methods in Medical Research Volume 5 (*Interscience Publishers Limited, London*)	57s
JACKSON, Q M, S R N A Handbook of Pædiatrics for Nurses in General Training (*H K Lewis & Co Ltd, London*)	9s net
JOSLIN, ELLIOTT P, A M, M D, SC D, ROOT, HOWARD F, M D, WHITE, PRISCILLA, M D, SC D, MARBLE, ALEXANDER, A M The Treatment of Diabetes Mellitus Ninth Edition (*Henry Kimpton, London*)	90s net
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KRUPP, MARCUS A, M D Physician's Handbook (*University Medical Publishers, Los Altos, California*)	$2 50
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TOBIAS, NORMAN, M D, Essentials of Dermatology (*J B Lippincott Company*)	48s net
WARREN, SHIELDS, M D, SC D, LECOMPTE, PHILIP M, M D The Pathology of Diabetes Mellitus (*Henry Kimpton, London*)	56s net
WHITE, JAMES C, M D, SMITHWICK, REGINALD H, M D, SIMEONE, FIORINDO A, M D The Autonomic Nervous System (*Henry Kimpton, London*)	90s net

INDEX

ABDOMINAL aorta, On occlusion of the, by C C Burt *et al* , 65, 113
Abortus fever, Some unusual manifestations of, by A W Branwood, 591
Adrenal cortex, Hormones of the, in clinical medicine, by E C Kendall, 1
Alimentary anomalies in infancy, 420
Anæmia, Iron absorption tests in the use of intravenous iron preparations, by Joan Crawley, 478
—— Megaloblastic, of pregnancy and the puerperium, by J R Clark, 274
Anæmias, megaloblastic, Thirty years' experience of the, by L S P Davidson, 315
Antibiotic substances, The assay of, 194
Antibiotics, The determination of bacterial sensitivity to, by J C Gould and J H Bowie, 178
Aorta, On occlusion of the abdominal, by C C Burt *et al* , 65, 113
Aortic embolism, 113
—— thrombosis, 71
Appendicitis, Acute, by I E W Gilmour and A G R Lowdon, 361
—— A study of 200 cases of, with special reference to their bacteriology, by A F Maccabe and J Orr, 100
Arterial disease, Plasma fibrinogen concentration in occlusive, by G I C Ingram, 94
Arthur, H R , and Chalmers, J D , Post partum blood pressure levels, 555
Asphyxia, The pathology of fœtal and neonatal, by Agnes R Macgregor, 229

BACTERIAL sensitivity to antibiotics, The determination of, by J C Gould and J H Bowie, 178
BCG vaccination as a public health measure, by A Wallgren, 161
Blood pressure levels, Post partum, by H R Arthur and J D Chalmers, 555
Blood, The eosinophile cells of the , a general review, by R D T Cape, 374
Borthwick, W M , Renal tuberculosis its pathogenesis and management in patients with extra urogenital disease, 583
Bowie, J H , *see* Gould, J C , and Bowie, J H , 178
Bramwell, Edwin, Obituary, 292
Branwood, A W , Carcinoma of the pancreas 28
Branwood, A W , Some unusual manifestations of abortus fever, 591
Brill Symmer's disease, 469
Bronchial asthma, 398
—— obstruction, 392
Bronchiectasis, Observations on the ætiology of, by N Wynn Williams, 427
Bronchoscopy, medical diagnosis and treatment, by I Malcolm Farquharson, 385
Burt, C C *et al* , On occlusion of the abdominal aorta, 65, 113

CAMERON, C , Tuberculosis an incident or a disease ? 143
Cancer, The history of human, by M Copisarow, 49
—— surgery, The case for wide resection in, by M R Ewing, 540
Cape, R D T , The eosinophile cells of the blood a general review, 374
Carcinoma of the bronchus, 386
—— —— pancreas, by A W Branwood, 28
Carmichael, N S , Obituary, 256
Carotene levels, Serum vitamin A and, in normal adults, by K D Lahiri and F J Scandrett, 39
Carotid sinus syndrome and carotid body tumour, by W Michie and R G Simpson, 443
Chalmers, J A , The vitamin B complex as a supplement in infant feeding, 247
Chalmers, J D , *see* Arthur, H R , and Chalmers, J D , 555
Chiene, G L , Obituary, 255
Clark, J R , Megaloblastic anæmia of pregnancy and the puerperium, 274
Clarkson, R D , Obituary, 156
Cochrane, R G , The influence of recent advances in leprosy on present day conceptions of the disease in relation to its diagnosis, treatment and prevention, 509
Copisarow, M , The history of human cancer, 49
Cranium and vertebral canal, Congenital deficiencies of the, 414
Crawley, Joan, Iron absorption tests in anæmia the use of intravenous iron preparations, 478

DAVIDSON, L S P , Thirty years' experience of the megaloblastic anæmias, 315
Dermatomyositis a case report, by H G H Richards, 327
Duguid, J P , *see* Wallace, A T , and Duguid, J P , 200

ENDOGENOUS lipid pneumonia, by H G Morgan, 261
Eosinophile cells of the blood, The , a general review, by R D T Cape, 374
Eosinophilic, The, respiratory syndrome, by E Soysa, 45
Ewing, M R , The case for wide resection in cancer surgery, 540

F 933, Application of, as a routine test in sustained hypertension, by D F Gibbs, 517
Farquharson, I Malcolm, Bronchoscopy, medical diagnosis and treatment, 385

Fœtal and neonatal asphyxia, The pathology of, by Agnes R Macgregor, 229

Gibbs, D F, Application of F 933 as a routine test in sustained hypertension, 517
Gilchrist, Elizabeth, and Tulloch, J A, Observations on the plasma fibrinogen content after myocardial infarction, 561
Gilmour, I E W, and Lowdon, A G R, Acute appendicitis, 361
Gould, J C, and Bowie, J H, The determination of bacterial sensitivity to antibiotics, 178
Griffith, Gwyn, Neurological complications of some infectious diseases, 492

Hodgkin's disease, 469
Hormones of the adrenal cortex in clinical medicine, by E C Kendall, 1
Hunter, A E, Obituary, 402
Hypertension, Application of F 933 as a routine test in sustained, by D F Gibbs, 517
—— Retinal changes in, by J Macaskill, 334

Infancy, Surgical emergencies of, by F H Robarts, 409
Infant feeding, The vitamin B complex as a supplement in, by J A Chalmers, 247
Infectious diseases, Neurological complications of some, by Gwyn Griffith, 492
Ingram, G I C, Plasma fibrinogen concentration in occlusive arterial disease, 94
Injuries, Peripheral nerve, by A J Slessor, 13
Intestinal obstructions in infancy, 415
Iron absorption tests in anæmia the use of intravenous iron preparations, by Joan Crawley, 478

James, T, Turner's syndrome in a male infant, 344

Kendall, E C, Hormones of the adrenal cortex in clinical medicine, 1

Lactation, The assessment of inadequate, by R A Miller, 238
Lahiri, K D, and Scandrett, F J, Serum vitamin A and carotene levels in normal adults, 39
Learmonth, Sir James, *see* Burt, C C *et al*, 65, 113
Lecture, The Frederick Price, Wallgren, A, 161
—— Cameron Prize, Kendall, E C, 1
Lectures, Honyman Gillespie
  Cameron, C, 143
  Clark, J R, 274
  Ewing, M R, 540
  Farquharson, I M, 385
  Macaskill, J, 334
  McCrie, J G, 297
  Macgregor, A R, 229
  Robarts, F H, 409
  Russell, W Ritchie, 530
Leprosy, The influence of recent advances in, on present day conceptions of the disease in relation to its diagnosis, treatment and prevention, by R G Cochrane, 509
Lowdon, A G R, *see* Gilmour, I E W, and Lowdon, A G R, 361

Macaskill, J, Retinal changes in hypertension, 334
Maccabe, A F, and Orr, J, A study of 200 cases of appendicitis with special reference to their bacteriology, 100
McCrie, J G, Reflections from a provincial Deanery, 297
McGibbon, J P, Obituary, 401
Macgregor, Agnes R, The pathology of fœtal and neonatal asphyxia, 229
McNeil, Charles, A student's notebook of James Syme's class of Clinical Surgery in 1861 62, kept by William McNeil with extracts and comments, 266
McNeil, William, A student's notebook of James Syme's class of Clinical Surgery in 1861 62, kept by, with extracts and comments by Charles McNeil, 266
Maternity hospital, *Staph aureus* air infection in a, by A T Wallace and J P Duguid, 200
Michie, W, and Simpson, R G, Carotid sinus syndrome and carotid body tumour, 443
Miller, R A, The assessment of inadequate lactation, 238
Morgan, H G, Endogenous lipid pneumonia, 261
Myocardial infarction, Observations on the plasma fibrinogen content after, by Elizabeth Gilchrist and J A Tulloch, 561

Neurological complications of some infectious diseases, by Gwyn Griffith, 492

Obituray
  Bramwell, Edwin, 292
  Carmichael, N S, 256
  Chiene, G L, 255
  Clarkson, R D, 156
  Hunter, A E, 402
  McGibbon, J P, 401
  Wallace, Sir David, 355
Occlusion of the abdominal aorta, On, by C C Burt *et al*, 65, 113
Orr, J, *see* Maccabe, A F, and Orr, J, 100

Pancreas, Carcinoma of the, by A W Branwood, 28
Parietes of the body cavities, Congenital deficiencies of the 412
Peripheral nerve injuries, by A J Slessor, 13
Plasma fibrinogen concentration in occlusive arterial disease, by G I C Ingram, 94
—— —— content after myocardial infarction, Observations on the, by Elizabeth Gilchrist and J A Tulloch, 561
Pneumonia, Endogenous lipid, by H G Morgan, 261
Poliomyelitis, by W Ritchie Russell, 530
Pregnancy and the puerperium, Megaloblastic anæmia of, by J R Clark, 274
Pulmonary abscess, 397
—— tuberculosis, 399

INDEX

Reflections from a provincial Deanery, by J G McCrie, 297
Renal function, Clearance tests of, by C P Stewart, 213
—— tuberculosis its pathogenesis and management in patients with extra urogenital disease, by W M Borthwick, 583
Respiratory syndrome, The eosinophilic, by E Soysa, 45
Reticuloses, The, and lymphoreticular sarcomas from the radiotherapist's point of view, by Margaret C Tod, 457
Retinal changes in hypertension, by J Macaskill, 334
Richards, H G H, Dermatomyositis a case report, 327
Richards, R L, *see* Burt, C C *et al*, 65, 113
Robarts, F H, Surgical emergencies of infancy, 409
Royal College of Physicians of Edinburgh, 208, 257, 357, 449
Royal College of Surgeons of Edinburgh, 108, 403, 449, 601
Russell, W Ritchie, Poliomyelitis, 530

SARCOMAS, The reticuloses and lymphoreticular, from the radiotherapist's point of view, by Margaret C Tod, 457
Scandrett, F J, *see* Lahiri, K D, and Scandrett, F J, 39
Sensitivity, Bacterial, to antibiotics, 178
Serum vitamin A and carotene levels in normal adults, by K D Lahiri and F J Scandrett, 39
Sheffield University Reflections from a provincial Deanery, by J G McCrie, 297
Simpson, R G, *see* Michie, W, and Simpson, R G, 443
Slessor, A J, Peripheral nerve injuries, 13
Society, Tuberculosis, of Scotland
  Borthwick, W M, 583
  Morgan, H G, 261
  Wimsett, W G, 573
Soysa, E, The eosinophilic respiratory syndrome, 45
Staph aureus air infection in a maternity hospital, by A T Wallace and J P Duguid, 200
Stewart, C P, Clearance tests of renal function, 213
Surgical emergencies of infancy, by F H Robarts, 409
Syme, James A student's notebook of his class of Clinical Surgery in 1861 62, kept by William McNeil with extracts and comments by Charles McNeil, 266

TOD, Margaret C, The reticuloses and lymphoreticular sarcomas from the radiotherapist's point of view, 457
Triple Qualification Board, 453
Tuberculosis an incident or a disease? by C Cameron, 143
—— The chemotherapy of urinary, by W G Wimsett, 573
—— Renal its pathogenesis and management in patients with extra urogenital disease, by W M Borthwick, 583
Tulloch, J A, *see* Gilchrist, Elizabeth, and Tulloch, J A, 561
Turner's syndrome in a male infant, by T James, 344

UNIVERSITY of Edinburgh, 108, 450
Urinary tuberculosis, The chemotherapy of, by W G Wimsett, 573
Uro genital conditions in infancy, 425
Urogenital, Extra, disease, Renal tuberculosis its pathogenesis and management in patients with, by W M Borthwick, 583

VACCINATION, BCG, as a public health measure, by A Wallgren, 161
Vitamin B complex, The, as a supplement in infant feeding, by J A Chalmers, 247

WALLACE, A T, and Duguid, J P, *Staph aureus* air infection in a maternity hospital, 200
Wallace, Sir David, Obituary, 355
Wallgren, A, BCG vaccination as a public health measure, 161
Wimsett, W G, The chemotherapy of urinary tuberculosis, 573
Wynn Williams, N, Observations on the ætiology of bronchiectasis, 427

BOOK REVIEWS

ABDOMEN The early diagnosis of the acute 10th ed by Z Cope 63
Alice and the stork by E Morland 61
Almeyda J Major symptoms in clinical medicine Vol II 111
Alvarez W C The neuroses 505
American College of Surgeons—Surgical Forum 1951 62
—— —— 1952 570
Anæsthesia The English pioneers of by F F Cartwright 405
Anæsthetics The mode of action of by T A B Harris 110
Anatomy and physiology Human 3rd ed by N D Millard and B G King 259
Anatomy Atlas of human new ed by F Froline *et al* 572
—— Cunningham s textbook of 9th ed ed J C Brash 160
—— Surgical 3rd ed by C L Callander ed B J Anson and W G Maddock 603
Annals of physical medicine. Vol I no 1 ed H Burt 504
Anson B J and Maddock W G (Eds) Surgical anatomy 3rd ed by C L Callander 603
Any questions? From the *British Medical Journal* 208
Apperley F L Patterns of disease as a basis of physiologic pathology 209
Asthmatic child The 2nd ed by G F Walker 406
Atlas A clinical of blood diseases 7th ed by A Piney 406
—— An of general affections of the skeleton by Sir T Fairbank 568
—— Color of morphologic hematology by G A Daland ed T H Ham 403
—— of histologic diagnosis in surgical pathology by K T Neubuerger and W T Wikle 210
—— of human anatomy new ed by F Froline *et al* 572

BAILEY Hamilton and Matheson Y M Emergency surgery Part IV 6th ed 507

Bailey P, and Von Bonin G The isocortex of man 61
Batchelor R C L and Murrell M Venereal diseases, described for nurses 110
Beaumont G E and Dodds E C, Recent advances in medicine, 13th ed, 571
Beaumont W Diathermy short wave therapy inductotherapy long wave therapy 2nd ed 259
Beck A C Obstetrical practice 5th ed, 406
Berman C Primary carcinoma of the liver 59
Bernstein L and Weatherall M Statistics for medical and other biological students 568
Bett W R Osler—the man and the legend 506
Black s medical dictionary 20th ed ed J D Comrie and W A R Thomson 63
Blood diseases A clinical atlas of, 7th ed, by A Piney 406
Blood groups Human and inheritance, by S D Lawler and L J Lawler 258
Books received 64 112, 212 260, 296 360 408, 456 508 572 604
Bortz E L Diabetes control 159
Bowley Agatha H Child care, 208
Braasch W F and Emmett J L Clinical urography—an atlas and textbook of roentgenologic diagnosis 208
Brain metabolism and cerebral disorders by H E Himwich 294
Brash J C (Ed) Cunningham s textbook of anatomy, 9th ed 160
Brazier Mary A B, The electrical activity of the nervous system 110
British Journal of Tuberculosis and Diseases of the Chest, ed P Ellman 258
British Medical Journal From the Any questions? 208
Brock R C The life and work of Astley Cooper, 454
Brockbank W Portrait of a hospital 602
Brompton Hospital Reports vol XIX 1950 209
Bronchial asthma—its relation to upper respiratory tract infection by R J Whiteman, 110
—— The management of, by H G J Herxheimer 453
Bronchitis Chronic by T Howell 158
Bull H C H X ray interpretation 2nd ed, 160
Burrows H Jackson and Coltart W D, Treatment by manipulation 2nd ed 359
Burt H (Ed) Annals of physical medicine Vol I no 1 504

Callander C L Surgical anatomy 3rd ed ed B J Anson and W C Maddock 603
Called to serve by P Gliddon and M Powell 569
Cardiac emergencies and heart failure by A M Master *et al* 569
Cartwright F F The English pioneers of anæsthesia, 405
Catarrh The rational treatment of by W Annandale Troup, 59
Catcheside D G The genetics of micro organisms 159
Cecil R L (Ed) The specialities in general practice, 258
Cecil R L and Loeb R F A textbook of medicine 8th ed 295
Celiac disease Management of by S V Haas and M P Haas 158
Cerebral cortex The postnatal development of the human Vol IV The cortex of the six month infant by J L Conel 62
Chamberlain E Noble A text book of medicine 109
Child care by Agatha H Bowley 208
Children Growth and development of, by E H Watson and G H Lowrey 60
Ciba Foundation Colloquia on Endocrinology Vol I, ed G E W Wolstenholme 569
Clark A J Applied pharmacology 8th ed, rev A Wilson and H O Schild 359
Clark W E Le Gros, The tissues of the body 3rd ed 408
Comrie J D and Thomson W A R (Eds), Black s medical dictionary, 20th ed 63
Conel J L The postnatal development of the human cerebral cortex Vol IV The cortex of the six month infant 62
Conybeare Sir J and Mann W N Textbook of medicine 10th ed, 571
Coope R The quiet art, 258
Cooper Astley The life and work of by R C Brock 454
Cope Z The early diagnosis of the acute abdomen 10th ed 63
—— The versatile Victorian 210
Cortisone and ACTH Untoward reactions of by V J Derbes and T E Weiss 403
Cripples, Central Council for the Care of Summary of legislation and directory of organisations for the care of the physically handicapped 358
Crosse V Mary The premature baby 3rd ed 508
Cunningham s textbook of anatomy, 9th ed, ed J C Brash, 160

Daland G A Color atlas of morphologic hematology ed T H Ham 403
Daley, R and Miller H G, Progress in clinical medicine 2nd ed 507
Darling M C R and Wilson T E Surgical nursing and after treatment 10th ed 63
Davidson M The diagnosis and treatment of intrathoracic new growths 358
Decompression sickness caisson sickness divers and flyers' bends and related syndromes by J F Fulton 404
Derbes, V J, and Weiss, T E Untoward reactions of cortisone and ACTH 403
Diabetes control by E L Bortz 159
Dianetics, by L R Hubbard 158
Diathermy short wave therapy, inductotherapy long wave therapy 2nd ed by W Beaumont 259
Dictionary, American illustrated medical 22nd ed by W A N Dorland 111
—— Black's medical, 20th ed, ed J D Comrie and W A R Thomson 63
Dilling W J The pharmacology and therapeutics of the materia medica, 63
Disease, Patterns of as a basis of physiologic pathology, by F L Apperly 209
Doctors by themselves by E F Griffith, 159
Dorland W A N American illustrated medical dictionary 22nd ed, 111
Dryerre H Aids to physiology, 4th ed, 295
Duke Elder, Sir Stewart Text Book of Ophthalmology Vol V, 568
Dyke S C Recent advances in clinical pathology, 2nd ed, 259

Ear, nose and throat diseases for the general practitioner by W McKenzie, 405
Ear nose and throat, Diseases of the, by G Portman 570
Electrocardiography Clinical unipolar by B S Lipman and E Massie, 159
Electroencephalography in clinical practice, by R S Schwab 158
Electron microscopic histology of the heart by B Kisch 109
Ellinger, T U H (Trans) Hippocrates on intercourse and pregnancy 569
Ellman P (Ed) The British Journal of Tuberculosis and Diseases of the Chest 258
Endocrine glands Diseases of the by L J Soffer 111
Endocrinology Ciba Foundation Colloquia on Vol I ed G E W Wolstenholme 569
—— The practice of 2nd ed by R Greene 160
Evans Sir C Lovatt (Ed) Principles of human physiology (Starling), 11th ed 603
Eye A pathology of the, 3rd ed by E Wolff, 63

Fairbank Sir T, An atlas of general affections of the skeleton 568
Feiling, A (Ed), Modern trends in neurology 59
Fellowship Examination Papers 1947 1951 For the Royal College of Surgeons, Edinburgh, 357
Fetus and the newborn Pathology of the, by E L Potter, 505
First aid to the injured and sick 19th ed (Warwick and Tunstall), rev A P Gorham, 360
Fisher J T and Hawley, L S, Diary of a psychiatrist, 601
Fletcher E Medical disorders of the locomotor system 2nd ed 64
Fœtal and neonatal pathology by J E Morison 455
Forensic medicine 2nd ed by K Simpson 507
Fractures and joint injuries 4th ed by Sir R Watson Jones Vol I 295
Fractures dislocations and sprains 5th ed, by J A Key and H E Conwell 112
French C N, The story of St Luke s Hospital 1750 1948 61
Froline F *et al* Atlas of human anatomy, new ed, 572
Fulton, J F Decompression sickness caisson sickness divers' and flyers bends and related syndromes 404

Geffen D H and Tracy S, Hygiene, infectious diseases and dietetics, 358

INDEX

Genetics of micro organisms The by D G Catcheside
159
Girdlestone G R and Somerville E W Tuber
culosis of bone and joint 2nd ed 507
Gliddon P and Powell M Called to erve 569
Glocumb C H (Ed) Rheumatic diseases Based
on the Proceedings of the Seventh International
Congress on Rheumatic Diseases 569
Goldberger E Heart disease its diagnosis and
treatment 60
Gordon E P and Shepherd W C ℞ for medical
writing 504
Gorham A P (Ed) Warwick and Tunstall s First
aid to the injured and sick 19th ed 360
Gray E A Portrait of a surgeon John Hunter 505
Greene R The practice of endocrinology 2nd ed
160
Greenhill J P Surgical gynecology 602
Greenhill J P and De Lee J B Principles and
practice of obstetrics new ed 211
Griffith E F Doctors by themselves 159
Gynecology Psychosomatic by W S Kroger and
S C Freed 357
—— Surgical by J P Greenhill 602

Haas S V and Haas M P Management of celiac
disease 158
Hall I Simson Diseases of the nose throat and ear
5th ed 359
Ham T H (Ed) Color Atlas of morphologic
hematology by G A Daland 403
Handfield Jones R M and Porritt Sir A E The
essentials of modern surgery 4th ed 61
Harris T A B The mode of action of anæsthetics
110
Health and the citizen by J V Walker 209
Heart disease its diagnosis and treatment by E
Goldberger 60
Hematology Clinical 3rd ed by M M Wintrobe
211
—— Color atlas of morphologic by G A Daland
ed T H Ham 403
Herxheimer H G J The management of bronchial
asthma 453
Himwich H E Brain metabolism and cerebral
disorders 294
Hippocrates on intercourse and pregnancy tr
T U H Ellinger 569
Histology Textbook of 6th ed by A A Maximov
and W Blook 508
Holmes G Introduction to clinical neurology
2nd ed 407
Hospital Portrait of a by W Brockbank 602
Howell T Chronic bronchitis 158
Hubbard L R Dianetics 158
Hunter John Portrait of a surgeon by E A Gray
505
Hygiene A synopsis of (Jameson and Parkinson)
10th ed by L Roberts and K M Shaw 359
—— infectious diseases and dietetics by D H Geffen
and S Tracy 358

Immunology 3rd ed by N P Sherwood 160
Intrathoracic new growths The diagnosis and treat
ment of by M Davidson 358
Isocortex of man The by P Bailey and G von Bonin
61

Jameson and Parkinson A synopsis of hygiene
10th ed by L Roberts and K M Shaw 359

Key J A and Conwell H E Fractures dislocations
and sprains 5th ed 112
Keynes G (Ed) The apologie and treatise of Ambroise
Paré containing the voyage made into divers
places with many of his works upon surgery 455
Kidney The Structure and function in health and
disease by H W Smith 404
Kisch B Electron microscopic histology of the
heart 109
Kleinberg S Scoliosis 506
Kolmer J A *et al* Approved laboratory technique
5th ed 407
Kranz J C and Carr C J The pharmacologic
principles of medical practice 2nd ed 406
Kroger W S and Freed S C Psychosomatic
gynecology 357
Krusen F H (Ed) Physical medicine and rehabilita
tion for the clinician 404

Laboratory diagnosis Clinical 4th ed by S A
Levinson and R P MacFate 260
Laboratory technique Approved 5th ed by J A
Kolmer *et al* 407
Lahey Clinic Surgical practice of the by Members
of the Staff of Lahey Clinic Boston 358
Law relating to hospitals and kindred institutions
Supplement to 1949 edition by S R Speller 110
Lawler S D and L J Human blood groups and
inheritance 258
Legislation and directory of organisations for the
care of the physically handicapped Summary of
compiled by the Central Council for the Care of
Cripples 358
Levinson S A and MacFate R P Clinical laboratory
diagnosis 4th ed 260
Life and death Between by H Williams 60
Lipman B S and Ma ie E Clinical unipolar
electrocardiography 159
Liver Primary carcinoma of the by C Berman 59
Locomotor system Medical disorders of the 2nd ed
by E Fletcher 64

McDonagh G E R The Nature of Disease Institute
62
McGawack T H The thyroid 111
McKenzie W Ear nose and throat diseases for the
general practitioner 405
Mackey H O A handbook of diseases of the skin 504
Mainland D Elementary medical statistics 570
Manipulation Treatment by 2nd ed by H Jackson
Burrows and W D Coltart 359
Manson Bahr Sir P Synopsis of tropical medicine
2nd ed 603
Martin Doyle J L C A synopsis of ophthalmology
294
Massage and remedial exercises 9th ed by N M
Tidy 571
Master A M *et al* Cardiac emergencies and heart
failure 569
Materia medica The pharmacology and therapeutics
of the 19th ed by W J Dilling 63
Maximov A A and Bloom W Textbook of
histology 6th ed 508
Medical Annual The 1951 ed Sir H Tidy and
A R Short 60
Medicine A text book of ed E Noble Chamberlain
109
—— —— 8th ed by R L Cecil and R F Loeb 295
—— Internal its theory and practice 5th ed by
J H Musser ed M G Wohl 407
—— Major symptoms in clinical Vol II by J
Almeyda 111
—— Progress in clinical 2nd ed ed R Daley and
H G Miller 507
—— Recent advances in 13th ed by G E Beau
mont and E C Dodds 571
—— Synopsis of tropical 2nd ed by Sir P Manson
Bahr 603
—— Textbook of 10th ed by Sir J Conybeare
and W N Mann 571
Mental diseases A new outlook on by F A Pickworth
455
Millard N D and King B G Human anatomy
and physiology 3rd ed 259
Miller S E A textbook of clinical pathology 4th ed
572
Monro T K The physician as a man of letters
science and action 209
Monroe R T Diseases in old age—a clinical and
pathological study of 7941 individuals over 61
years of age 453
Moore R A A textbook of pathology 2nd ed 259
Morison J E Fœtal and neonatal pathology 455
Morland E Alice and the stork 61
Mulligan R M Syllabus of human neoplasms 257
Musser J H Internal medicine its theory and
practice 5th ed rev M G Wohl 407

Nature of Disease Institute The by G E R
McDonagh 62
Neoplasms Syllabus of human by R M Mulligan 257
Nervous system Di ease of the 7th ed by F M R
Walshe 571
—— The electrical activity of the by Mary A B
Brazier 110
Neubuerger K T and W T Wikle Atlas of histologic
diagnosis in surgical pathology 210
Neurology A synopsis of by Tatlow Ardis and
Bickford 504
—— Introduction to clinical 2nd ed by G Holmes
407
—— Modern trends in ed A Feiling 59
Neuroses The by W C Alvarez 505
Neurosurgery Essentials of by L C Oliver 506

Nose throat and ear, Diseases of, 5th ed, by I Simson Hall 359
Nursing Surgical and after treatment 10th ed, by M C R Darling and T E Wilson, 63

OBSTETRICAL practice, 5th ed, by A C Beck, 406
Obstetrics Principles and practice of new ed, by J P Greenhill and J B De Lee 211
Ogilvie, Sir H and Thomson W A R (Eds), Practical procedures 2nd ed The Practitioner Handbooks 407
Old age Diseases in—A clinical and pathological study of 7941 individuals over 61 years of age by R T Monroe 453
Oliver L C Essentials of neurosurgery 506
Ophthalmology by A E Town 294
—— A synopsis of by J L C Martin Doyle 294
—— Systemic by A Sorsby 210
—— Text Book of Vol V, by Sir Stewart Duke Elder 568
Oral and dental diseases, 2nd ed by H H Stones, 211
Osler—the man and the legend by W R Bett 506
Overend, W E, The use of tracer elements in biology, 405

PARÉ Ambroise The apologie and treatise of containing the voyage made into divers places, with many of his works upon surgery, ed G Keynes, 455
Pathology, A textbook of 2nd ed, by R A Moore, 259
—— A textbook of clinical 4th ed, by S E Miller, 572
—— Recent advances in clinical, 2nd ed, ed S C Dyke 259
Pharmacologic principles of medical practice, The, 2nd ed by J C Krantz and C J Carr 406
Pharmacology Applied 8th ed by A J Clark, ed A Wilson and H O Schild 359
Physical medicine and rehabilitation for the clinician, ed F H Krusen 404
Physician, The, as a man of letters science and action, by T K Monro 209
Physiology, Aids to 4th ed by H Dryerre 295
—— Principles of human (Starling), 11th ed, ed Sir C Lovatt Evans, 603
Pickworth, F A, A new outlook on mental diseases, 455
Piney, A, A clinical atlas of blood diseases 7th ed, 406
Portman G, Diseases of the ear nose and throat, 570
Potter E L Pathology of the fœtus and the newborn 505
Practical procedures 2nd ed The Practitioner Handbooks ed Sir H Ogilvie and W A R Thomson 407
Premature baby The 3rd ed by V Mary Crosse 508
Psychiatrist Diary of a by J T Fisher and L S Hawley 601
Psychiatry in general practice, by C A H Watts and B M Watts, 505

QUIET art, The, by R Coope 258

℞ for medical writing, by E P Gordon and W C Shepherd, 504
Rhesus factor, The 3rd ed by G F Roberts 456
Rheumatic diseases Based on the Proceedings of the Seventh International Congress on Rheumatic Diseases ed C H Glocumb 569
Rivlin S M The treatment of varicose veins 61
Roberts, G F, The Rhesus factor 3rd ed 456
Roberts L, and Shaw K M (Eds) A synopsis of hygiene, 10th ed (Jameson and Parkinson), 359
Royal College of Surgeons Edinburgh Fellowship Examination Papers 1947 1951, 357

ST LUKE'S Hospital, The story of 1750 1948 by C N French 61
Sand, R, The advance to social medicine 405
Schwab R S Electroencephalography in clinical practice 158
Scoliosis by S Kleinberg 506
Sellors T H and Livingstone J L Modern practice in tuberculosis 2 vols, 454
Sherwood N P Immunology, 3rd ed 160
Short A R, Wonderfully made, 61
Simpson, K, Forensic medicine, 2nd ed, 507
Skeleton An atlas of general affections of the, by Sir T Fairbank 568
Skin A Handbook of diseases of the, by H O Mackey, 504
Smith, Homer W, The kidney Structure and function in health and disease 404
Social medicine The advance to by R Sand, 405
Soffer L J Diseases of the endocrine glands, 111
Sorsby A Systemic ophthalmology, 210
Specialities in general practice, The, ed R L Cecil, 258
Speller, S R Law relating to hospitals and kindred institutions Supplement to 1949 edition, 110
Starling's Principles of human physiology, 11th ed, ed Sir C Lovatt Evans, 603
Statistics, Elementary medical, by D Mainland 570
—— for medical and other biological students, by L Bernstein and M Weatherall, 568
Stomach and duodenum Surgery of the, by C E Welch, 62
Stones H H Oral and dental disease, 2nd ed, by H H Stones, 211
Surgery Emergency Part IV, 6th ed, by H Bailey and N M Matheson, 507
—— The essentials of modern 4th ed, by R M Handfield Jones and Sir A E Porritt, 61
Surgical Forum—American College of Surgeons 1951, 62
—— —— 1952, 570
—— pathology Atlas of histologic diagnosis in by K T Neubuerger and W T Wikle, 210
—— practice of the Lahey Clinic, by Members of the Staff of Lahey Clinic Boston, 358

TARLOW, Ardis and Bickford, A synopsis of neurology, 504
Thyroid The, by T H McGavack 111
Tidy Sir H and Short, A R (Eds) The Medical Annual 1951 60
Tidy N M, Massage and remedial exercises, 9th ed, 571
Tissues of the body, The, 3rd ed, by W E Le Gros Clark 408
Town, A E, Ophthalmology, 294
Tracer elements in biology, The use of by W E Overend 405
Troup, W Annandale The rational treatment of catarrh 59
Tuberculosis Modern practice in ed T H Sellors and J L Livingstone 2 vols 454
Tuberculosis of bone and joint, 2nd ed, by G R Girdlestone and E W Somerville 507
Tuberculosis schemes in Great Britain and the Commonwealth Handbook of, 13th ed, 111

UROGRAPHY Clinical—An atlas and textbook of roentgenologic diagnosis, by W F Braasch and J L Emmett 208

VARICOSE veins The treatment of by S M Rivlin, 61
Venereal diseases Described for nurses By R C L Batchelor and M Murrell, 110
Victorian, The versatile, by Z Cope 210

WALKER G F The asthmatic child 2nd ed, 406
Walker, J V Health and the citizen 209
Walshe, F M R, Diseases of the nervous system, 7th ed 571
Warwick and Tunstall's First Aid to the injured and sick 19th ed ed A P Gorham 360
Watson E H, and Lowrey G H Growth and development of children 60
Watts C A H and Watts, B M, Psychiatry in general practice 505
Welch C E Surgery of the stomach and duodenum, 62
Whiteman, R J Bronchial asthma—its relation to upper respiratory tract infection 110
Williams Harley Between life and death 60
Wilson A, and Schild H O (Eds), Applied pharmacology, by A J Clark 8th ed 359
Wintrobe M M Clinical hematology 3rd ed 211
Wohl, M G (Ed) Internal medicine its theory and practice, 5th ed, by J H Musser 407
Wolff E A pathology of the eye 3rd ed 63
Wolstenholme G E W (Ed) Ciba Foundation Coloquia on Endocrinology Vol I, 569
Wonderfully made by A R Short 61

X RAY interpretation, 2nd ed, by H C H Bull 160

The Transactions of the Medico-Chirurgical Society of Edinburgh

SESSION CXXXI—1951-1952

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The Transactions of the Medico-Chirurgical Society of Edinburgh

DYSPHAGIA WITH SPECIAL REFERENCE TO CARDIOSPASM

By JAMES M GRAHAM, Ch M , LL D , F R C S Ed

IT is usual for the retiring President to offer to the members, in the form of a valedictory address, some reflections on a subject of his own choosing With the latitude allowed on these occasions, I have ventured to choose a clinical subject and will refer to certain of the conditions which cause dysphagia and particularly to cardiospasm and the late results of treatment for this condition

The surgery of the œsophagus scarcely existed in my early days Recent advances date from the publication in 1913 by Thorek of his account of the first successful removal of a carcinoma of the thoracic œsophagus His patient not only survived the operation but lived for thirteen years without recurrence

My own interest in this branch of surgery dates from 1917, when, in the absence of my chief, Professor Alexis Thomson, I was called upon to undertake the list of operations Amongst the cases was one recommended by Dr Logan Turner, who was present at the operation It was an epithelioma of the hypopharynx involving the upper end of the œsophagus I had not seen such a case operated on and had no knowledge of the technique required After removal of the affected segment it was impossible to reconstitute the gullet, and it was necessary to leave the upper end of the œsophagus anchored in the neck It was only by a combination of good fortune and beginner's luck that the patient not only made a good recovery but has remained well ever since I have ventured to mention this case again as it is certainly unusual to be able to report a case operated on for malignant disease, particularly in this area, alive and well thirty-four years after operation (Fig 1)

Since then I have operated on other cases of this kind, and in 1926 I had the opportunity for the first time of performing the plastic operation recommended by Wilfrid Trotter by which the defect in the gullet was repaired by a skin flap Good fortune attended this case too, for I am happy to record that Mrs J is still alive and well, swallowing

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Valedictory address by the President, read at a meeting of the Medico-Chirurgical Society of Edinburgh on 24th October 1951 normally, twenty-five years after removal of an epithelioma of the hypopharynx Of the 16 cases in which this operation was completed, 3 lived long enough to be regarded as cured

Few if any of these cases have been operated on in recent years It is worth considering whether there is not still a place for operation in cases of carcinoma of the hypopharynx in preference to treatment by irradiation Professor McWhirter informs me that he has a record of 91 cases of carcinoma of the hypopharynx treated by X-ray therapy in the Royal Infirmary , of this number 4 are still alive at intervals of from four to twelve years after the treatment

My former house surgeon, Dr T M Prossor, now on the staff of the Westminster Hospital, informs me that at that hospital between 1935 and 1947 there were 56 cases of post-cricoid cancer treated of which 53 have been followed up These cases were all treated by gamma irradiation on the 4-gram teleradium unit and some in addition had at the same time high voltage X-ray treatment Fifty of the 53 patients followed up had died in less than three years and 3 patients had survived for periods of from five to sixteen years

It is obvious that carcinoma of the hypopharynx is not very radiosensitive, and I am inclined to think that operation should be recommended in the first place when removal of the disease appears to be feasible The case with advanced disease should still be treated by irradiation If, as is probable, there is no satisfactory evidence of immediate regression, operation could still be considered in a proportion of these cases

I should like now to mention the first case of pharyngeal pouch on which I operated, as it illustrates a rare complication The patient, Mr S , an elderly gentleman, had struggled on for many years until he was unable to swallow anything He was fibrillating and in such poor condition that he was fit only for a gastrostomy in the first instance Two weeks later diverticulopexy, the first stage of a two-stage operation for removal of the pouch, was performed After the operation the patient developed pneumonia and an empyema for which drainage was required The second stage of the operation was indefinitely postponed as the patient's symptoms were completely relieved by the high fixation of the pouch There was, however, a limit to the good fortune in this case, as six years later he returned with an epithelioma which had begun in the pouch and was already inoperable and involving the skin The case emphasises the importance of removal of the pouch which is essential as a rule for complete relief of symptoms

Recent advances have now made it safe to remove the pouch in one stage The only occasion when a two-stage operation may still be advisable is in the case of a very large pouch extending into the mediastinum, for there is always a chance that leakage will occur a few days after the operation (Fig 2)

A similar but much rarer type of diverticulum occurs in relation to the lower third of the œsophagus, projecting usually to the right, a short distance above the diaphragm It is commonly referred to as an epiphrenic diverticulum A patient, Mr MacD , aet 55, with this type of diverticulum, had been under observation for ten years before operation for its removal seemed justified There was no real dysphagia and the patient complained mainly of discomfort due to distension of the pouch which could be relieved by washing it out with an œsophageal tube When the symptoms became more persistent three years ago, an operation for its removal was undertaken by the transpleural route on the right side The pouch, which was about the size of a goose's egg, was removed without difficulty No leakage followed the operation The patient made a good recovery and has remained well (Fig 3)

CARDIOSPASM

The main facts regarding cardiospasm are well known It is of interest mainly because of the doubtful ætiology and in regard to the problems of treatment

(1) There is marked dilatation and hypertrophy of the œsophagus without organic stenosis

(2) The lower end of the œsophagus from the hiatus in the diaphragm to the cardiac orifice appears to be normal

(3) There is no paralysis of the œsophageal wall, for irregular and sometimes *excessive peristalsis occurs and the muscle coats are hypertrophied*

(4) Some form of neuro-muscular disorder is obviously responsible for the obstruction to the passage of food immediately above the cardia

There is no anatomical sphincter at the lower end of the œsophagus Knight has shown, however, that the circular muscle coat from the level of the hiatus to the cardia acts as a physiological sphincter which is controlled by the vagus and the sympathetic That the arrest in the passage of food in cardiospasm is due either to spasm or to failure of relaxation of the physiological sphincter is proved by the fact that the obstruction is relieved by division of the circular muscle fibres in this area The absence of any sign of hypertrophy of the circular muscle fibres seems to me to confirm Hurst's original suggestion that the condition present is an achalasia or failure of relaxation rather than spasm

That local and persistent spasm of non-striped muscle in the alimentary tract leads to gross hypertrophy I have seen in the colon In a male patient, aet 60, with diverticula of the pelvic colon, localised spasm at the site of the diverticula led to such a degree of muscle hypertrophy that a tumour-like mass formed which closely simulated a malignant tumour and caused almost complete obstruction of the colon As a result of the rest following colostomy, the muscle hypertrophy so completely disappeared that at a subsequent laparotomy no trace of the supposed tumour could be found and the colostomy was closed The patient remained well for five months after closure of the colostomy, but gradually thereafter the symptoms of obstruction recurred, and when the patient was readmitted to hospital it was found necessary to perform a colostomy again The cause of the obstruction was again found to be due to a tumour in the same situation, similar in every way to the tumour previously observed The patient died after the operation, and at the post-mortem examination it was shown by the late Dr James Dawson that only drops of water could be forced through the obstructed area The tumour proved on naked-eye and microscopical examination to be formed solely by a gross hypertrophy of the fibres of the circular muscular coat associated with the presence of minute diverticula

High bilateral vagotomy in the cat causes a condition resembling cardiospasm in man In the absence of vagal function the tone of the physiological sphincter persists , the œsophagus dilates and fills with food and the animal slowly starves That the tone is maintained by the sympathetic was proved by Knight (1934-35a) when he showed that after vagotomy division of the sympathetic fibres to the lower end of the œsophagus was followed by relaxation of the sphincter and complete relief of the obstruction to swallowing

In recent years bilateral vagotomy has frequently been performed for the relief of symptoms due to duodenal and anastomotic ulcers. Following this operation, the patient may suffer considerable discomfort from loss of gastric tone and occasionally complains also of slight temporary dysphagia There is no suggestion, however, that cardiospasm is due to a lesion either central or peripheral of the vagi , all the evidence points to the vagi being normal in these cases

Hurst suggested that the neuro-muscular imbalance with apparent sympathetic over-activity might be due to a lesion of the ganglion cells of Auerbach's plexus It is known that these ganglion cells form a cell station in the vagal pathway The absence or the loss of these cells could be expected to interfere with the vagal impulse Following Hurst's suggestion, Rake (1927) of Guy's Hospital examined several early specimens of achalasia and stated that the ganglia in the lower part of the œsophagus showed inflammatory changes or were even replaced by fibrous tissue

The problem was investigated by Lendrum (1937) working with material from the Mayo Clinic He examined in great detail a series of thirteen specimens which had been collected over a period of years While stressing the wide variation in the number of ganglion cells in the normal œsophagus, he recorded a striking loss or a complete absence of the ganglion cells in Auerbach's plexus in all his cases of cardiospasm Some support for the theory that a reduction in ganglion cells is responsible for the changes in cardiospasm is afforded by the facts recently established in connection with Hirschsprung's disease of the colon It has been shown that the ganglion cells of the myenteric plexus are absent from the rectum and pelvic colon distal to the dilated loop Unfortunately Hirschsprung's disease and cardiospasm, with many features in common, are not strictly comparable, for there is no evidence that cardiospasm is congenital as true Hirschsprung's disease definitely is

The main difficulty in settling the facts regarding the integrity of the ganglion cells in cardiospasm is due to the lack of specimens available for examination I was aware of only two specimens in the Anatomical Museum of the University which I used to demonstrate to my class of surgical pathology many years ago One of these is of historical interest as it was presented by Dr Alexander Wood over a hundred years ago and was described by him in the *Edinburgh Medical Journal* , it has been sufficiently preserved for microscopical examination Professor Drennan of the Pathology Department has provided other four specimens, one of which was from a case of my own, and these have been examined by Dr Rae Lyon, to whom I am indebted for the following report

" *Examination of Ganglia at Cardio œsophageal Junction in 5 Cases of Cardiospasm*

" Using slight modification of Lendrum's technique where the ganglia cells were enumerated in a measured vertical strip of œsophagus immediately adjoining the stomach, 5 specimens were examined and compared with a control series which had 7 89 ganglion cells per cm

" The oldest, though it had been preserved for a very long time, had fully retained the histological features and details, yet neither ganglia nor any traces of ganglia cells were observed

" The second case, with hypertrophy and dilatation of the œsophagus, had 11 3 ganglion cells per cm

" A specimen from Mr Graham's own series had two adjacent blocks of tissue examined , one had 12 6 ganglion cells per cm , the other had only 4 6 ganglion cells per cm

" One section was taken from a case of syphilitic aortitis to demonstrate leukoplakia and hypertrophy of the œsophagus Only three ganglia could be discovered which gave an average of 0 8 ganglion cells per cm

" Finally, at a recent autopsy the hypertrophied œsophagus was examined in three separate sites and in each there were over ten ganglion cells per cm

" Thus, in comparing the 5 cases with the normal obtained from a control series, ganglion cells were reduced or absent in 2 specimens , 2 had more than the average number of cells and from the final case adjacent strips gave one result above normal, and the other below

" *Conclusions*

" 1 In this limited series the constant reduction or absence of the ganglion cells of Auerbach's plexus reported by Lendrum and others has not been observed

" 2 Except in the oldest specimen, no stretches of œsophagus, devoid of ganglia, were discovered, nor were there present dense nerve bundles, such as were found by Bodian, indicating that there is no direct relationship between cardiospasm and Hirschsprung's disease

" 3 Though this series is small, the cases appear to be divisible into groups with an average number of ganglion cells and those with a marked reduction

"4 The great variation in ganglion cell counts, even between serial sections, suggests that unless innumerable sections are cut, this method of investigation has no great accuracy in assessing the number or condition of the ganglia in Auerbach's plexus"

Although a reduction in the ganglion cells of Auerbach's plexus in cardiospasm is an attractive theory, it must be admitted that the evidence so far produced is inconclusive and that the cause of cardiospasm is still uncertain

DIAGNOSIS

This can usually be established easily by the history and the characteristic X-ray appearances of the œsophagus An œsophagoscopic examination should settle any doubtful problems

X-RAY EXAMINATION

In a typical case the œsophagus is dilated and fusiform in outline with the lower end at the level of the diaphragm In advanced cases the degree of dilatation is excessive Peristalsis is active in the earlier stages while at the same time irregular and ineffective The regular waves which follow the act of swallowing tend to fade as they pass downwards and fail to reach the lower end In the lower two-thirds of the œsophagus the normal waves are frequently replaced by irregular contractions and by superficial waves of tertiary type These irregular contractions tend to persist and to recur unlike the peristaltic waves in the normal œsophagus which correspond only to individual acts of swallowing When dilatation is very marked, only momentary tertiary waves are likely to remain and these may finally cease The smooth fusiform outline of the dilated œsophagus reaching to the level of the diaphragm, the irregular peristalsis and the limited passage of barium and in addition the absence of the usual gas bubble in the stomach are characteristic of the condition

DIFFERENTIAL DIAGNOSIS

Although the diagnosis can usually be established easily, an œsophagoscopic examination should be carried out as a routine, it is essential when the diagnosis is doubtful and is required in most cases as a preliminary to treatment by dilatation The short history and steady deterioration of the patient's condition usually suggest the cause of the dysphagia in cases of carcinoma When the dysphagia is due to carcinoma, the œsophagus is seldom greatly dilated and there is no great retention of food as in cardiospasm In most cases of carcinoma of the lower end of the œsophagus and of the cardiac end of the stomach the diagnosis is obvious on X-ray examination Occasionally the appearance of the dilated œsophagus in cardiospasm may be simulated by a localised carcinoma of the cardiac end of the stomach which has

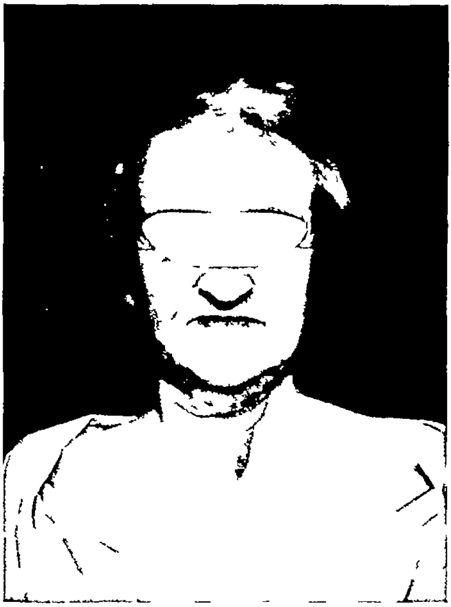
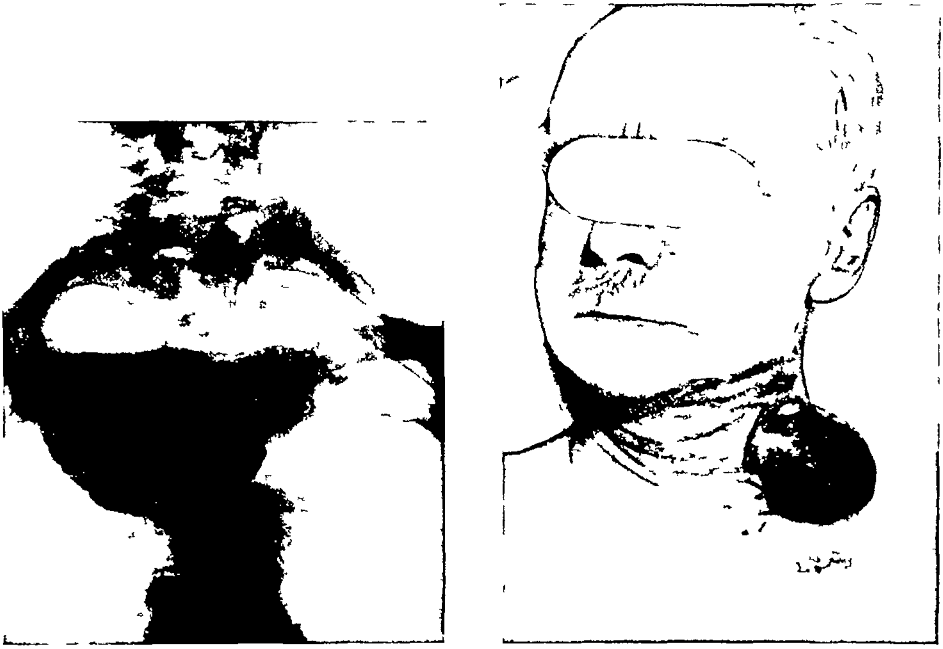


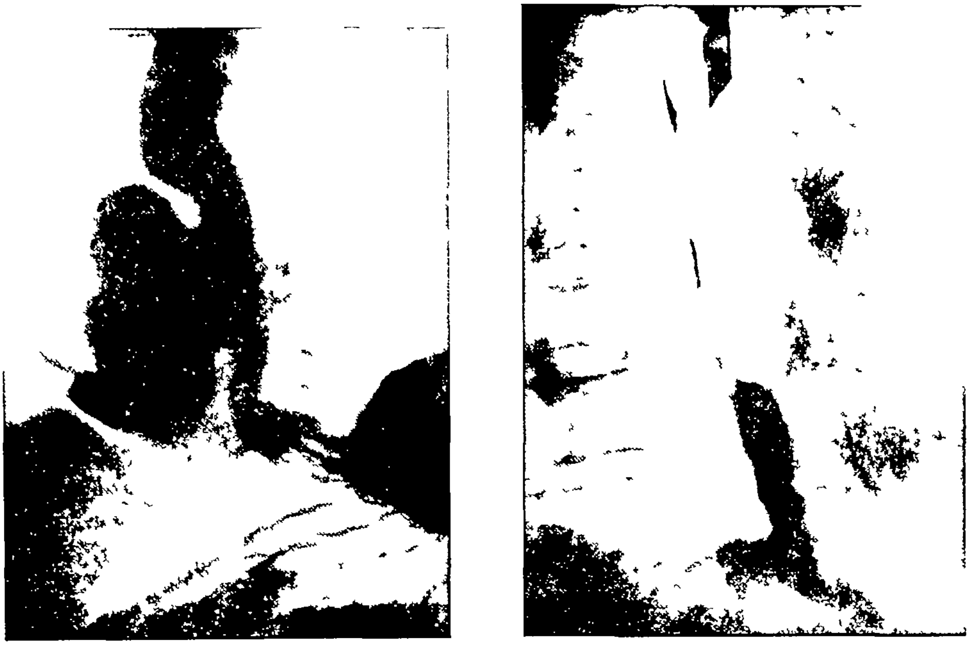
FIG 1 —Mrs M Thirty four years after removal of an epithelioma of the hypopharynx, showing the œsophagus implanted in the neck



A

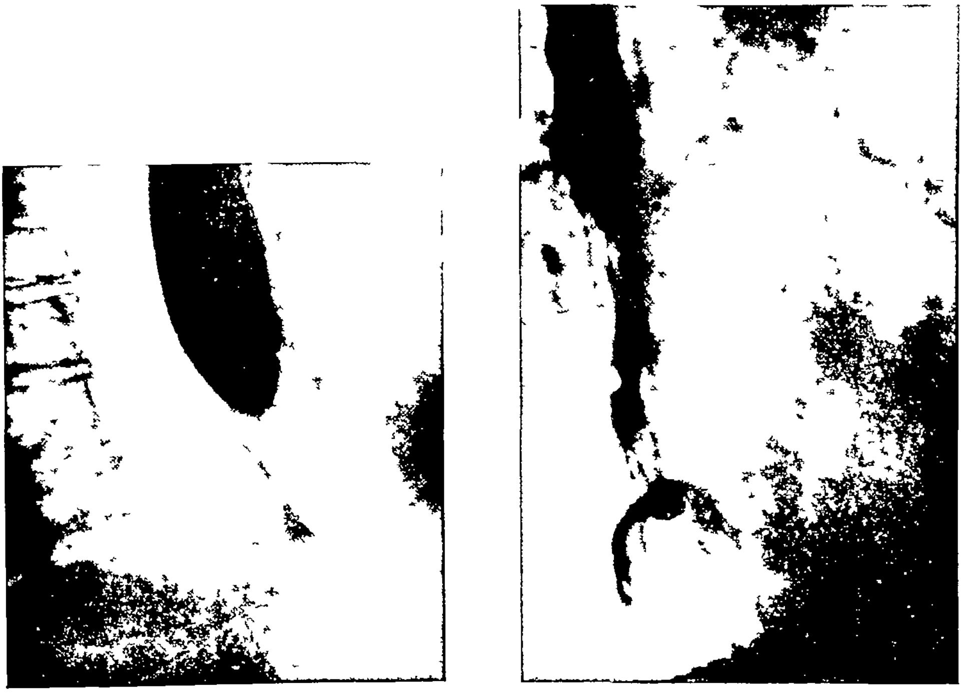
B

FIG 2 —Large pharyngeal diverticulum A Before operation, B showing the first stage



A B

FIG 3 —Mr MacD Case of epiphrenic diverticulum A Before, and B after removal



A B

FIG 4 —Mr M A Dilatation of the œsophagus with dysphagia due to peptic ulceration B The same case showing peptic ulceration and a hiatal hernia.

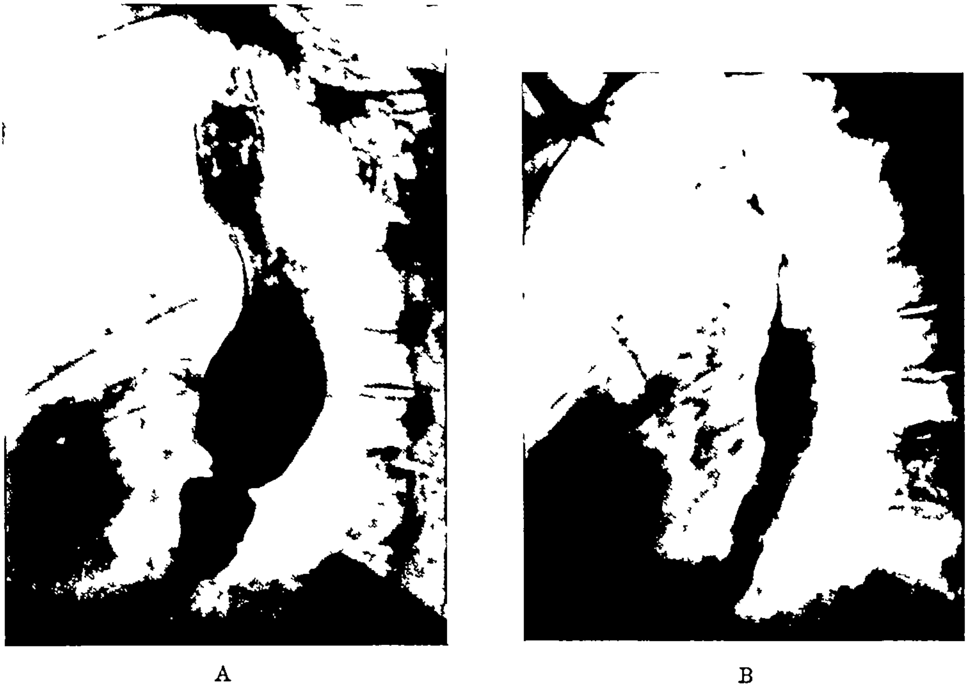


FIG 5—Mrs B Case of cardiospasm A Before, and B after treatment with a Negus dilator The œsophagus is reduced in size but still shows some irregular peristalsis

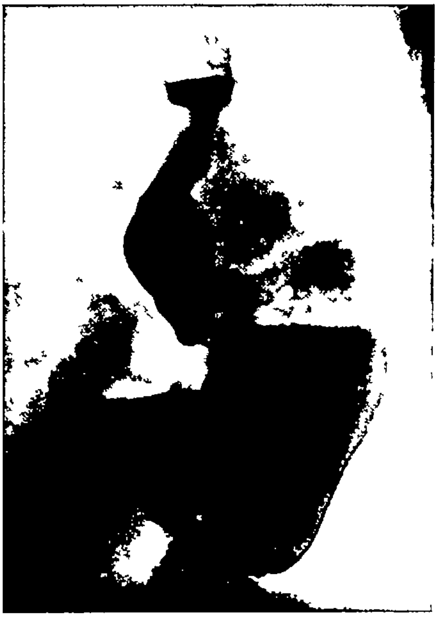
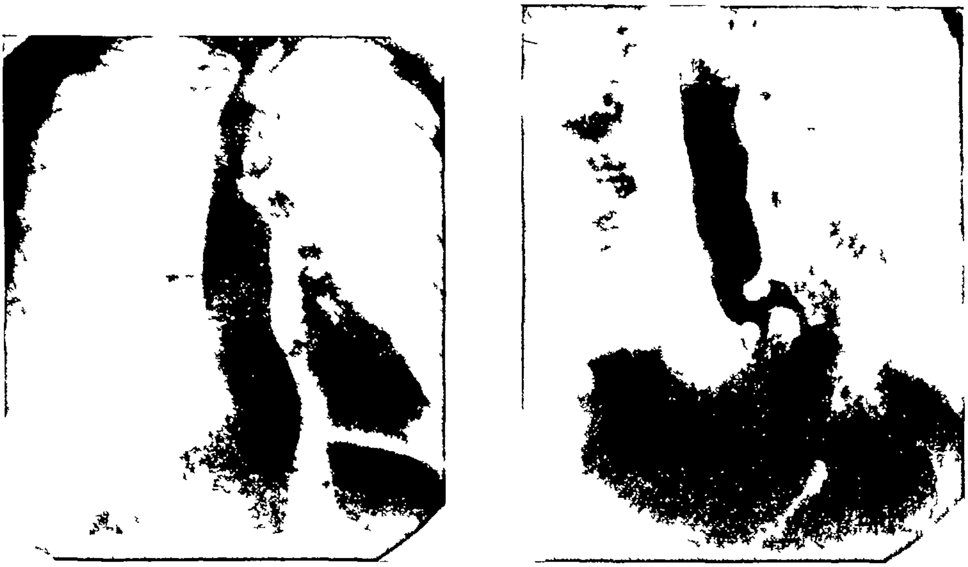
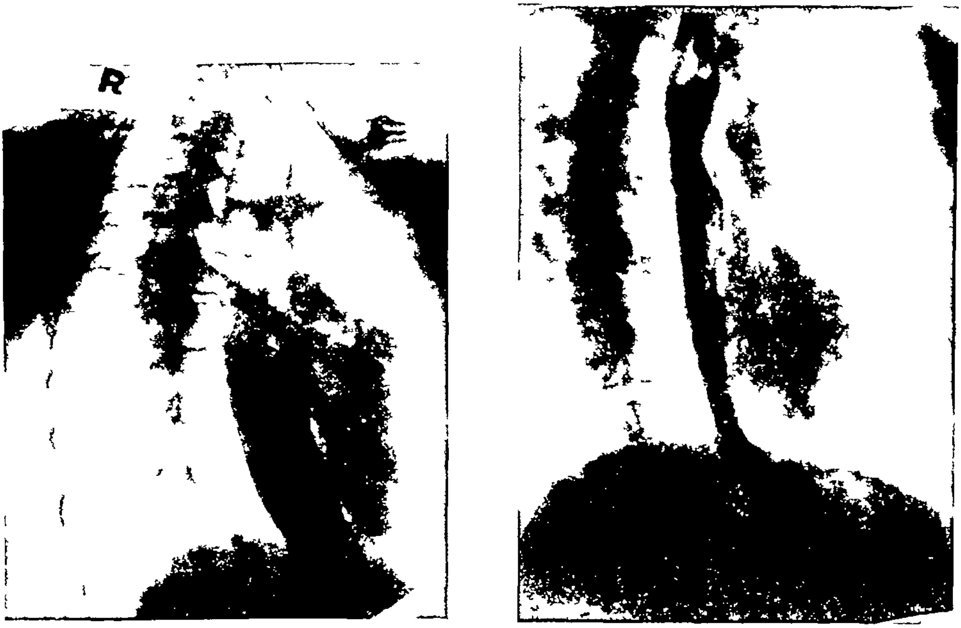


FIG 6—J F Case of cardiospasm fifteen years after treatment by manual dilatation Complete relief of symptoms with a gain of 5 stones in weight Œsophagus still dilated with some irregular peristalsis



A B

FIG 7 —Mrs N Case of cardiospasm A Before, and B after œsophago gastrostomy, showing still some dilatation of the œsophagus



A B

FIG 8 —G M Case of cardiospasm A before, and B after Heller's operation The œsophagus is restored almost to a normal size and the symptoms are completely relieved

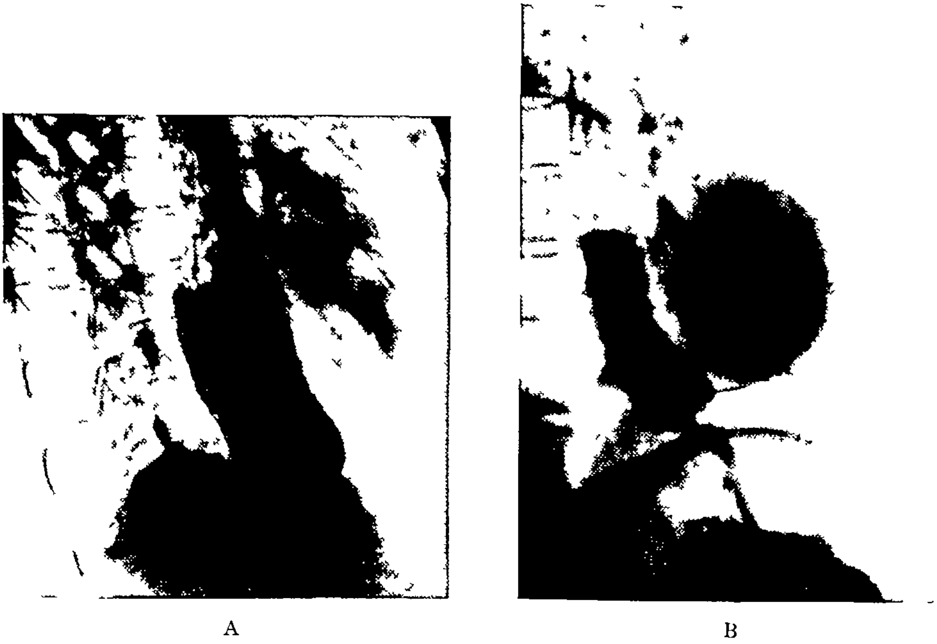


FIG 9—J McD Case of cardiospasm A Before, and B after Heller's operation Symptoms completely relieved but still slight delay in emptying and tertiary waves present Gas bubble present after operation

infiltrated the lower end of the œsophagus without producing a filling defect on radiological examination

A case of dysphagia, referred to me by Dr Greig Anderson as a probable carcinoma of the cardiac end of the stomach, illustrated the difficulty occasionally met with in determining the diagnosis The appearance of the X-ray plate suggested cardiospasm and an œsophagoscopic examination was inconclusive as it had not been possible either to pass the œsophagoscope through the cardia or to obtain a positive biopsy A further X-ray examination of the patient in the Trendelenburg position confirmed the clinical diagnosis of carcinoma and a transpleural resection was successfully performed It is interesting to note that this patient from whom more than half of the stomach as well as the lower end of the œsophagus was removed five years ago, has recently suffered from a hæmatemesis due to peptic ulceration at the lower end of the œsophagus A test meal in this case shows that there is an absence of free HCl in the resting gastric juice but that later free HCl appears, no doubt as a result of the action of hormonal secretion from the pyloric end of the stomach It is instructive to know that free HCl can still be secreted in a case of carcinoma of the stomach after an extensive resection when both vagi have been divided

If a diagnosis of cardiospasm is sometimes suggested by the X-ray appearance of the œsophagus in a case of carcinoma, I have also known cases in which through inadequate investigation the opposite mistake has been made and carcinoma has been diagnosed instead of cardiospasm A middle-aged woman appeared in my out-patient clinic many years ago and asked to have her gastrostomy tube changed The operation of gastrostomy had been done elsewhere five years before for a supposed carcinoma at the lower end of the œsophagus Œsophagoscopic examination showed that a moderate degree of cardiospasm was present and the instrument was easily passed into the stomach After adequate dilatation the patient was able to swallow normally and later the gastrostomy was closed Contrary to expectation, the patient was far from grateful It appeared that she was a gypsy travelling the country with a show, and that she used to entertain the public with some sort of a performance with her gastrostomy tube, posing as " the woman with the rubber stomach " She seemed to regret that her source of livelihood had been removed

There is seldom any difficulty in differentiating simple strictures Occasionally in cases of peptic ulceration at the lower end of the œsophagus the patient will complain of difficulty in swallowing and it will be necessary to distinguish this cause of dysphagia from carcinoma or cardiospasm The dysphagia due to œsophagitis or peptic ulceration may be mainly or entirely due to spasm, but in chronic cases there is the possibility of an organic stenosis as a result of fibrosis X-ray examination will show moderate dilatation of the œsophagus with a stenosis some distance above the diaphragm with smooth walls tapering fairly rapidly In most cases a hiatal hernia is present, and it is possible when sufficient barium has entered the stomach and the patient is recumbent with the head lowered, to demonstrate the presence of a pouch of stomach above the level of the diaphragm The œsophagoscope and a biopsy will settle the diagnosis in almost all doubtful cases

My first case of peptic ulcer of the œsophagus in which a clinical diagnosis was made illustrates the extreme degree of dysphagia which may be due to œdema and spasm without organic stenosis The case was referred from a medical ward in 1936

Mr M , aet 50 Dysphagia without pain had been present for three months, and for two weeks the patient had been unable to swallow anything The radiologist had examined the patient some weeks before and had reported a malignant stricture He had been œsophagoscoped a few days before I saw him and the preliminary report seemed to confirm the diagnosis—later it was reported that the tissue removed was inflammatory After a gastrostomy the patient's capacity for swallowing gradually returned and a fresh X-ray examination revealed the presence of an ulcer crater and a hiatal hernia (Fig 4) After eighteen months the gastrostomy tube was removed as the ulcerated area had healed The patient has remained well , he has symptoms of a duodenal ulcer and suffers occasionally from heartburn, but has had no recurrence of dysphagia

TREATMENT

Treatment by dilatation should be employed in every case in the first instance The day of the mercury bougie is past Experience shows that the sphincteric area can be most satisfactorily stretched by a hydrostatic dilator in the form introduced by Plummer at the Mayo Clinic and by Negus in this country (Fig 5)

Approximately 70 per cent of the cases are symptomatically cured by dilatation with one or other of these instruments According to Olsen, Harrington, Moersch and Andersen (1951) of the Mayo Clinic, satisfactory results are obtained in 75 per cent of cases and only 20 per cent cannot be relieved permanently by dilatation Maingot (1949) has found operation necessary in 10 per cent of cases treated with the Negus dilator Johnstone and Wooler (1949) state that in a series of 46 cases treated by the Negus dilator 35 patients were completely relieved of dysphagia while in 8 cases the treatment failed or was unsatisfactory Success with these forms of dilator depends upon the successful rupture of the circular muscle fibres at the lower end of the œsophagus There is a risk, although a small one, of rupture of the œsophagus

The indications for operation can be defined as failure of dilatation to relieve the symptoms or when it is impossible to introduce the dilator

Mikulicz Operation —Till recently the most popular operation was digital dilatation of the lower end of the œsophagus introduced by Mikulicz in 1904 The success of the operation depends upon the stretching and rupture of the muscle fibres at the narrow lower end of the œsophagus The operation, however careful the technique, is not an aseptic one

I have performed the operation in 5 cases One patient died after the operation He was too exhausted for almost any form of surgical interference At the post-mortem examination the cardia was found to be successfully dilated and there was no rupture or sepsis One of my patients gained 5 stones in weight and has remained free of dysphagia for fifteen years (Fig 6) The dysphagia returned, however, in 2 of the cases There are no indications now for this operation as its objects can be more safely achieved by other means

Sympathectomy (*Knight's Operation*)—From his experimental work, Knight (1934-35b) suggested that a sympathectomy below the diaphragm should be tried in cardiospasm Mr W A D Adamson was the first to perform this operation and his case was a brilliant success I tried Knight's operation in 2 cases, both of which were failures Other surgeons have had the same experience The failure of the operation is no doubt due to the fact that the sympathetic nerve supply to the lower end of the œsophagus in man is much more extensive than in the experimental animal Professor Mitchell of Manchester, while still attached to the Anatomy Department in Aberdeen, showed that in addition to the branches of the cœliac plexus the lower end of the œsophagus receives many branches from above the level of the diaphragm I think the subsequent history of Mr Adamson's case suggested to him the probability that the dysphagia had been due to peptic ulceration and spasm The patient undoubtedly had an ulcer diathesis and the stenosis in the œsophagus was some distance above the diaphragm

Œsophago-gastrostomy Cardioplasty—These operations have frequently been performed in recent years, particularly in the United States In most cases the operation has been performed by the transpleural route

With this route the new or enlarged opening remains above the level of the diaphragm and not only the sphincteric control at the cardia but the pinch-cock action of the diaphragm is lost When the cardia becomes incompetent in this way, acid contents tend to regurgitate from the stomach, particularly when the patient is lying down, and peptic ulceration is likely to occur in the lower end of the œsophagus

Recently Barrett and Franklin (1949-50) have reviewed the results of their cases including 17 cases of œsophago-gastrostomy and 6 cases of cardioplasty The immediate results of their operation were excellent The main object of their paper, however, was to draw attention to the unsatisfactory late results and to condemn these operations In their experience these operations often produce more serious symptoms than the original condition, and they attribute the harmful results entirely to the free communication between the stomach and the œsophagus After a period of from three to six months symptoms appeared in most of their cases, such as pain, bleeding, anæmia and recurrence of dysphagia Of 17 cases in which the operation of œsophago-gastrostomy had been done, only 3 were well and relieved of their previous symptoms My own experience of œsophago-gastrostomy is limited to one case which in regard to the subsequent history was similar to the cases recorded by Barrett and Franklin

Heller's Operation —This operation corresponds closely to Rammstedt's operation for congenital pyloric stenosis As originally described by Heller in 1913, the circular muscle coat of the œsophagus in the constricted area was divided by vertical incisions on both anterior and posterior aspects A single anterior incision has since been found to be adequate The operation has been practised to a considerable extent in France, but is seldom referred to in American literature In this country it has been employed as the method of choice in recent years by Barlow, Maingot and Allison It can be performed either by the abdominal or the transpleural route Like most general surgeons, I have used the abdominal route The operation can be completed safely and as a rule easily through an abdominal incision Thoracic surgeons prefer the transpleural route and this method should certainly be selected when difficulty in exposure of the cardia below the diaphragm is anticipated The circular muscle fibres are thin and the greatest care is needed to avoid puncturing the mucosa The incision for division of the muscle fibres should extend from a point immediately on the gastric side of the cardia to the point where the dilatation of the œsophagus begins at the upper level of the hiatus in the diaphragm The retraction of the circular muscle coat on each side is much greater than would be expected, and a wide area of mucosa is exposed so thin that the contents can be seen moving within the lumen of the œsophagus

Results of Heller's Operation —There is sufficient evidence from records published in recent years to prove that the immediate effects of Heller's operation are satisfactory It is important to know what the late results are likely to be In this connection I have some evidence to offer for my cases have been reviewed on two occasions, almost four years ago and again recently when Mr Gilmour and Dr MacKenzie of the Radiology Department kindly examined the patients for me

The operation was performed in 13 cases One patient died following the operation The fatal case was a man of 36 who had twice previously been operated on for the same condition He had been treated by sympathectomy below the diaphragm and by Mikulicz's operation He was much relieved by the digital dilatation but the dysphagia recurred and he was admitted to hospital three years later in poor condition The operation was difficult owing to adhesions The patient did well for forty-eight hours but then collapsed and died following the perforation of a gastric ulcer Such an unusual complication could not occur in a straightforward case

The remaining 12 cases have been available for review In one case, Mrs N , the division of the muscle fibres was incomplete and much too limited and the operation necessarily failed to relieve the symptoms

Before the division of the circular muscle fibres was completed, a small tear appeared in the exposed mucosa as a result of traction on the stomach The closure of the opening was perhaps more thorough than was needed To make certain that there would be no leakage, the divided muscle was sutured together again

It was surprising that the patient was completely relieved of dysphagia for some months When the symptoms returned, no relief was obtained with a hydrostatic dilator and a transpleural œsophago-gastrostomy was performed (Fig 7) Again the dysphagia was completely relieved but only for a time, as œsophagitis developed as described by Barrett and Franklin

Fortunately her symptoms are at present in abeyance and for a period of a year she has been well apart from slight anæmia, and has been free of dysphagia

In December 1946, 10 of the cases were examined and X-rayed, at intervals of from one year to four years after Heller's operation All of the patients were in good condition and well, with an average gain of 2 stones in weight All were able to take a full normal diet None had had any difficulty in swallowing and no regurgitation had occurred in any of the cases (Fig 8) The fact that there is no tendency to œsophagitis and peptic ulceration after Heller's operation was confirmed in this series of cases at this time and during the later review The patients without exception were well pleased with the result of the operation and very grateful for the relief obtained

The same cases have recently been reviewed again, together with one additional case operated on three and a half years ago The operation had been performed over eight years previously in 4 of the cases, over seven years in 3 cases, over six years in 2 cases, over five years in one case and over three years in the case reviewed for the first time The most recent case, operated on 13th January 1948, had gained 6 stones in weight and was free of symptoms

All of the 10 cases previously reviewed were in good health with the increase in weight following operation well maintained Since the previous review, however, 3 of the patients have developed occasional slight symptoms

Mrs G , aet 51 Operation on 30th April 1945 This patient had suffered at intervals from dysphagia over a period of fifteen years and from severe dysphagia and frequent regurgitation of food after every meal during the previous year She had remained perfectly well for five years after operation and was able to eat anything without any difficulty, and this is still the case except that during the last six months she has felt occasional discomfort after eating meat of any kind Apart from this item of food, she can eat anything without discomfort and her weight has been maintained At the X-ray examination on 27th June 1951 the barium was seen to pass through freely into the stomach The œsophagus, however, did not empty completely and marked irregular peristalsis was noted and at the end of half an hour there was still a trace of barium in the œsophagus

Mrs M , aet 51 The symptoms in this case had been present for one year before operation on 15th April 1946 Difficulty was felt with both fluids and solids and there was frequent regurgitation after meals The patient was free of all symptoms for a period of five years after the operation She still feels well and her weight is maintained Recently at intervals of five or six weeks she has had a sensation of wind in the epigastrium dispelled by a glass of warm water This sensation has been felt particularly when she has been worried At the X-ray examination on 26th May 1951 barium passed readily into the stomach There was still some dilatation of the œsophagus and the degree of peristalsis in the lower two-thirds was greater than normal Intermittent contractions came and went with great rapidity and were much more obvious during screening than in the films There was still a trace of barium in the œsophagus for half an hour but the patient had no discomfort

Mrs MacP , aet 75 This patient was seen first in 1927 when she was X-rayed by the late Dr Hope Fowler and a diagnosis was made of cardiospasm in an early stage She had been treated intermittently with the mercury bougie without much benefit An X-ray examination eight years ago showed that the œsophagus had become greatly dilated and peristalsis was very inactive A small diverticulum had formed a short distance above the diaphragm Six years ago she was sent from the north of Scotland by ambulance as an emergency case It was considered doubtful if she would stand the journey For some time she had been able to take very little nourishment She was dehydrated, fibrillating and very feeble Dr Gillies thought a general anæsthetic was out of the question I gave her a local anæsthetic with a view to gastrostomy Once before I had exposed the lower end of the œsophagus with local anæsthesia and had demonstrated a chronic peptic ulcer above the diaphragm by pulling down the œsophagus In this case also, after infiltrating the abdominal wall and the lesser omentum, I was able to expose the lower end of the œsophagus At this stage the patient was given a small dose of pentothal and the operation was completed within a few minutes The patient was able to swallow freely from the first and remained symptom-free till a few months ago Since then at rare intervals she has felt discomfort in swallowing solids such as meat or fish Her weight is maintained at 8 stones 10 lb as compared with 6 stones before the operation, and at the age of 75 she is still able to lead a normal and active life

All 3 patients were typical cases of cardiospasm and had been completely free of symptoms for over five years Each felt at intervals of a few weeks slight discomfort in swallowing solids such as meat All 3 patients were in good health and apart from these occasional lapses were able to take a full diet without any difficulty The remaining 8 cases were entirely relieved of their dysphagia None had to eat slowly and there had been no suggestion of regurgitation in any of the post-operative cases

The fact that slight symptoms had reappeared in 3 cases, after a long interval, emphasises the importance of determining the remote results in the evaluation of any method of treatment in this particular condition

X-ray Examination —Some evidence which may help to explain the recurrence of symptoms is afforded by the X-ray examination of the cases in this series, particularly in regard to the size and emptying of the œsophagus after a barium meal

In contrast to the appearance before operation, there was a well-defined gas bubble in the fundus of the stomach The absence of a gas bubble in cases of cardiospasm before operation is no doubt due to the large quantity of retained food and fluid in the gullet

There was invariably a rapid entry of barium into the stomach whether a thin or a thick medium was given In all except in 2 of the cases in which the œsophagus had been greatly dilated there was a marked reduction in the calibre of the œsophagus which sometimes returned almost to a normal size

An almost constant abnormality present was the tendency of the barium to remain longer than usual in the œsophagus, sometimes for a few minutes or even for half an hour

When there is only a small amount of barium retained, the peristalsis may be almost normal, when the delay is more marked, irregular tertiary waves predominate and there may be some retrograde peristalsis (Fig 9)

The fact that there is some delay in emptying of the œsophagus after the dysphagia has been relieved is not appreciated by the patient, he differs in this respect from a normal individual with thick barium in the œsophagus who is conscious of its presence and gets rid of it by repeated acts of swallowing

The cause of the delay in emptying of the œsophagus is not apparent It may be that there is still some trace of obstruction unrelieved by the operation, perhaps due to too limited division of the muscle or to scar tissue

An explanation worthy of consideration is that peristalsis in the œsophagus is abnormal in cardiospasm Irregularities in peristalsis seen before operation suggest that the inco-ordination is not confined to the area of the sphincter The same slight delay in emptying of the œsophagus was observed in my case of œsophago-gastrostomy soon after the operation, although barium was freely entering the stomach through an ample stoma I have seen a different picture when the œsophago-gastrostomy has been done after resection of a malignant stricture at the cardia, in such a case, when the previously dilated œsophagus is otherwise normal, the barium may flow so rapidly into the stomach that it is difficult to visualise the œsophagus, although this can readily be done when the patient is recumbent and tilted so that the barium flows back into the œsophagus

The tendency of the dilatation of the œsophagus to persist in advanced cases of cardiospasm is in striking contrast to the restoration of the stomach to a normal size after a simple pyloric stenosis has been relieved by operation

In nearly all the descriptions in the literature regarding the results of the various operative procedures employed in cardiospasm, reference is made to the fact that the radiological appearance of the œsophagus seldom shows an improvement corresponding to the relief of symptoms

The delay in emptying of the œsophagus and the irregular peristalsis present are sufficient to account for the discomfort or occasional slight difficulty in swallowing referred to in the cases with recurrent symptoms

Why these patients have symptoms is not apparent when it is recognised that some of the other cases with almost similar radiological findings are free of symptoms as these patients were till recently One of the 3 patients with symptoms, a lady of 75, had had a greatly dilated œsophagus with minimal peristalsis for many years, and in her case the size of the œsophagus was little altered after the operation

CONCLUSIONS

From these observations it seems justified to conclude that Heller's operation, properly performed, offers a good prospect of relieving the symptoms due to cardiospasm

It should be preferred to other surgical measures when treatment by dilatation has failed The immediate results of the operation are excellent, but in certain cases after a lapse of years there is a tendency for symptoms to return

Peristalsis in the œsophagus is abnormal in cases of cardiospasm, and even when the dysphagia has been completely relieved by operation and the œsophagus is reduced in calibre, there is frequently some delay in the final passage of barium into the stomach

The transpleural route is to be preferred if difficulty in exposing the œsophagus is anticipated from adhesions or from any other cause The exposure for Heller's operation by the abdominal route is relatively easy in thin patients and this route should be selected when the patient is feeble and in specially poor condition

I am indebted to Mr I E W Gilmour and Dr John MacKenzie for the most recent review of my cases, and to Dr Rae Lyon for the detailed examination and report on five specimens of cardiospasm I am also indebted to Professor R McWhirter and to Dr T M Prossor for their statements regarding the results of radiotherapy in carcinoma of the hypopharynx

REFERENCES

BARRETT, N R, and FRANKLIN, R H (1949-50), *Brit Journ Surg*, 37, 194
JOHNSTONE, A S, and WOOLER, G H (1949), *Postgrad med Journ*, 25, 203
KNIGHT, G C (1934-35a), *Brit Journ Surg*, 22, 155
KNIGHT, G C (1934-35b), *Brit Journ Surg*, 22, 864
LENDRUM, F C (1937), *Arch intern Med*, 59, 474
MAINGOT, R (1949), *Postgrad med Journ*, 25, 187
OLSEN, A M, HARRINGTON, S W, MOERSCH, H J, and ANDERSEN, H A (1951), *Journ Thoracic Surg*, 22, 164
RAKE, G W (1927), *Guy's Hosp Rep*, 77, 146

A REVIEW OF INFECTIOUS DISEASES DURING THE FIRST HALF OF THIS CENTURY

The Incidence of Infectious Diseases 1900-1950

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In presenting these reflections on the changes which have occurred in the common fevers over the first half of this century I have confined myself to these as they unfolded themselves in the Edinburgh City Hospital For my information I have relied on the annual reports of my predecessors, C B Ker from 1900-24, W T Benson from 1925-36, and my own reports from 1937 onwards As many of the cases coming into hospital were admitted for social and clinical reasons, for example a large number of our measles and whooping cough patients were sent in because of poor home conditions or because of severity of attack, the figures which I put before you are not to be regarded as exact vital statistics Nevertheless they may be regarded as giving a fair picture of the ebb and flow of the principal communicable diseases in Edinburgh I propose therefore to give a brief survey of these decade by decade

The First Decade —The hospital report of 1901 records that typhus and smallpox were still to be encountered but were numerically on the wane, so that in 1901 there were 14 typhus cases with no deaths and 5 smallpox cases with 1 death Typhus flickered on in twos and threes for a year or two but was never more to be a menace in Edinburgh although it lingered for some years longer in the sister burgh of Leith Smallpox was only dormant for in 1904 a sharp epidemic comprising 170 cases with 15 deaths afflicted the city However this was Edinburgh's last experience of variola on any large scale, and although limited outbreaks occurred in 1908 (20 cases with no deaths), 1920 (9 cases with no deaths) and 1942 (36 cases with 8 deaths), the disease has never assumed the severity that it had done in 1893-95 when there were 697 cases with 73 deaths As a matter of fact in 1901, as judged by the numbers of patients brought into hospital, the principal infectious diseases were measles (626 cases with 9 5 per cent fatality), scarlet fever (601 cases with 3 3 per cent fatality), diphtheria (364 cases with 7 6 per cent fatality), whooping cough (174 cases with 25 8 per cent, fatality), enteric fever (166 cases with 10 8 per cent fatality), and erysipelas (116 cases with 8 6 per cent fatality) As we shall see, with changing epidemiological and clinical fortunes, these, excepting enteric, were to remain the chief contributors to hospital admissions and the main preoccupation of those in medical charge for nearly the

Address given at a meeting of the Medico-Chirurgical Society of Edinburgh on 7th November 1951 whole period under review Enteric has been mentioned as an exception and it was during this decade that it fell into the background, 93 cases with 5 deaths being recorded in 1906, and 30 cases with 3 deaths in 1911 A temporary alteration in the picture was provided in 1907 when Edinburgh had its first experience of cerebrospinal fever in epidemic form, 112 cases with 88 deaths being recorded in that year What these must have cost the medical and nursing staff in effort and anxiety is revealed by the comment that treatment was drainage by lumbar puncture, hot baths, and various serums, the most effective being the hot baths However, a supply of serum sent by Flexner of New York gave encouraging results in a limited number of cases

The Second Decade—Unfortunately no annual reports were published during the first world war but from what statistics are available, and particularly those of 1911 and 1921, scarlet fever, diphtheria, measles, whooping cough, and erysipelas were as usual by far the greatest contributors to the hospital admissions During the latter years of the first decade the increase in diphtheria admissions had been giving rise to some concern, and in 1911 there were 558 cases with a 7 5 per cent fatality Ten years later, although the severity of attack as estimated by case fatality (6 6 per cent) had not increased, the total of 908 diphtheria admissions with 60 deaths was calculated to maintain that concern

The Third decade—Although the hospital was well accustomed to admitting large numbers of cases of scarlet fever its resources were extended in 1921 as a result of a milk outbreak in Leith which brought the total annual admissions for that disease to 1983 It will give some idea of the sudden calls which may be made on a fever hospital when I mention that 529 of these patients were brought into hospital in one month (July) Apart from its prevalence some anxiety was caused in 1923, 1924 and 1925 lest the disease should be returning to the virulent type experienced in the seventies and eighties of the previous century, as the case fatality during these years remained relatively high at over 5 per cent As a side-light on this severity I reported that in 1924, among 1604 cases of scarlet fever, nephritis occurred as a complication in 79, and of these 11 died, a nephritis case fatality of 13 9 per cent However these fears were not realised although since the early twenties scarlet fever has continued to make by far the greatest contribution to our admissions In the early twenties also there were the great recurring influenza epidemics and in 1922 influenza cases accounted for approximately one-tenth of the annual admissions, 450 cases with a 14 8 per cent case fatality Although in succeeding years sharp outbreaks of influenza have occurred the hospital has never since been called upon to face emergencies on that scale Also about this time a new disease appears in the records, epidemic encephalitis, but, although a most interesting condition, it never amounted to much numerically The largest number of cases seen in any one year was 14 in 1923, and although the disease continued to appear sporadically in the wards up to 1930, by that time it had virtually gone All through the decade

1920-30 the predominant diseases as usual were scarlet fever, diphtheria, measles, whooping cough and erysipelas, but towards the end of that period a newcomer thrust its way upwards in the list of the principal diseases in the shape of puerperal sepsis This was not of course a new disease, a few cases had always found their way into the City Hospital annually, but admission to hospital began to be sought on an ever-widening scale as the result of the introduction of the puerperal pyrexia regulations Thus we find that in 1931 there were 130 confirmed cases of this condition with an 11 5 per cent case fatality, and a relatively high admission rate of between 150 and 200 cases per annum was to continue to absorb the attention of the medical and nursing staffs till comparatively recent times In the early twenties the change in type of infecting organism in enteric began to show itself Up till that time typhosus infections were the rule, but in 1922 out of 15 cases 3 were paratyphosus B Since then paratyphoid B infections have progressively increased until at the present time, among the few enterics encountered, it is most unusual to find a true typhoid That enteric could not be regarded entirely as a disease of the past is shown by sharp outbreaks of 57 cases in 1927 and another of 71 cases in 1929, both of paratyphoid B fever I have already drawn attention to the steadily mounting admissions for diphtheria throughout the second decade, and this persisted in the third decade so that in 1929 1135 cases, and in 1930 1086 cases were treated in hospital In both these years the number of diphtheria cases narrowly exceeded those of scarlet fever but this was the high-water mark of the disease in recent times and never since have diphtheria admissions been anywhere near these figures

The Fourth Decade —Again this period continued to be dominated by scarlet fever, diphtheria, measles, whooping cough, erysipelas and puerperal sepsis, scarlet fever and diphtheria being outstanding Indeed in 1933 confirmed cases of scarlet fever treated in hospital reached the unprecedented figure of 3461, easily a record in the history of the hospital, and this was apparently due to an all-round epidemic prevalence during the year, and not to any particular incident such as a milk outbreak Fortunately the high total of admissions was not accompanied by an increase in fatality and the percentage of fatal cases was well below 1 per cent for the whole of the decade and indeed was below 0 5 per cent in the latter half Although after the high prevalence in 1929 and 1930 diphtheria continued to diminish on the whole towards the latter part of the decade, case fatality continued to remain high between 5 and 8 per cent for the various years An interesting feature of the disease at this time was the diminution in the number of cases of the laryngeal type, whereas in 1930 and 1931 these had numbered 97 and 57 respectively, in 1938 and 1939 they had dwindled to only 17 and 7 cases A comparative newcomer which appeared on the scene in the thirties was bacillary dysentery and confirmed cases mounted from 33 in 1933 to 101 in 1939 Cerebrospinal fever remained quiescent, never reaching more than 20 cases per annum in the last half of the decade One interesting feature of the epidemic situation was the appearance of poliomyelitis in any number, 21 cases in 1936 and 22 in 1938 Measles mortality showed a sharp fall to 0 73 per cent in 1939—it had moved between 5 and 10 per cent, for years previously—and from that time onwards the decline has been progressive In 1939 there was a large drop in our total admissions owing to the dispersal of the juvenile population at the outbreak of war

The Fifth Decade—This has probably been the most memorable in the history of the hospital It began with heavy years in 1940 and 1941, all the common diseases contributing their quota, but outstanding being the epidemics of cerebrospinal fever with 317 cases in 1940 and 211 in 1941 The mitigating feature of these outbreaks, however, was that the case fatality had been brought down from approximately 70 per cent to well under 20 per cent, thanks to the sulphonamides Looking at the period as a whole the most notable feature was the virtual disappearance of diphtheria The number of cases fluctuated between 671 in 1940 and 387 in 1945, but thereafter a well marked decline set in and the figures are worth giving in detail —1946, 188 cases with case fatality of 6 38 per cent, 1947, 51 cases with 1 96 per cent case fatality, 1948, 18 cases with 5 55 per cent case fatality, 1949, 7 cases with no deaths, and in 1950, 2 cases with no deaths In parenthesis it may be said that so far in 1951 we have not seen a single case Scarlet fever behaved in rather an extraordinary way also in this period, falling from 1535 admissions in 1942 to 238 in 1947 This last was the lowest number of scarlet fever admissions ever recorded at the City Hospital, but a sharp uprise has occurred since then and in 1950 we were over the 1000 mark once more It should be mentioned also that in the five years 1946-50 inclusive there has not been a single scarlet fever death The decline in the measles mortality noted as setting in in the fourth decade has persisted, and in 1950 among 269 cases there was not a single death As regards the other killing diseases there has been a marked drop in the admissions of puerperal sepsis, so that in 1949 and 1950 only 26 and 9 cases respectively came into hospital and there were no deaths Erysipelas cases have also much diminished and there have been no deaths among a total of 81 cases admitted in 1949 and 1950 Whooping cough still presents a challenge, however, and while the case fatalities ranging from 10 to 20 per cent or over prevailing up till the early forties are no longer experienced, it is a good year even now when the proportion of deaths is under 5 per cent Apart from the decline in morbidity and mortality witnessed in the diseases mentioned one important event in the decade was the smallpox outbreak of 1942, which left a lasting impression on all who had anything to do with it Then we had the poliomyelitis outbreak of 1947 with 173 cases and a 12 per cent fatality which was our share of the first really widespread epidemic in this country Although relatively quiescent in 1948 and 1949 the disease flared up again in 1950 so that we had 89 cases admitted to hospital The rise in admissions of bacillary dysentery to 597 and 482 in 1944 and 1945 was also of some interest although from the standpoint of severity and case fatality these infections have never been an urgent problem Finally, since 1948 we have devoted a good deal of attention to infantile gastroenteritis and well over 100 cases per annum are now admitted Our fatality in 1948 was the discouraging one of 17 per cent, but we have done somewhat better in 1950 with a case fatality of 3 17 per cent in 126 cases

From this brief outline it will be apparent that scarlet fever, diphtheria, measles, whooping cough, and erysipelas were our main preoccupation over the greater part of the first half century Sharp outbreaks of such diseases as enteric and cerebrospinal fever occasionally obtruded themselves, but it was only from the late twenties onwards that new problems appeared on any scale in the shape of bacillary dysentery, puerperal sepsis, poliomyelitis, and infantile gastroenteritis Puerperal sepsis and gastroenteritis were not of course new diseases, and it was as a result of administrative action rather than epidemiological change that these diseases became important in fever hospital practice Quantitatively therefore, until the latter half of the fifth decade, apart from the great decline in enteric which had taken place in the first decade, there was not a great deal of change except the change in character that individual epidemic diseases assume from time to time, *e g* a particularly high incidence of a severe form of nephritis as a complication of scarlet fever has been mentioned as occurring in 1924, or again, over a limited period, an undue proportion of cases of one or other of the exanthemata will exhibit aberrant rashes which in themselves will run true to type and manifest a curious atypical sameness These cyclic changes in clinical character and severity are characteristic of epidemic disease In the latter half of the fifth decade of course quantitatively the changes have been remarkable, particularly in respect of the disappearance of diphtheria, the fall almost to vanishing point of puerperal sepsis, and the rise of poliomyelitis

Even with full recognition of these quantitative changes it is in the qualitative aspects of the common fevers that the most impressive alterations have occurred, and in none have these been better exemplified than in scarlet fever Right through the first half of this century there has been a progressive diminution in severity of scarlet fever, and it is important to note that this decline was operating well before the introduction of the potent remedies which have energed in the last few years As evidence of the decline in severity we can look to the disappearance of the malignant or toxic, and the septic or anginose forms of the disease For example, in 1924 in a total of 1604 cases there were 19 of the toxic variety with 16 deaths, and 34 of the septic variety with 16 deaths, but over the next few years first the toxic and then the septic type disappeared and from 1930 onwards the disease was seen only in the simplex form It should not be assumed, however, from its nomenclature that the simplex type was without its problems, since complications even in this form of the disease were frequent and relatively constant in incidence, and that they were serious can be appreciated from the fact that in the years 1933-36 inclusive 113 mastoidectomies were performed among 7276 patients suffering from scarlet fever At the present time, no doubt owing to the introduction of penicillin, the necessity for performing this operation has practically disappeared Other common complications such as acute otitis media, adenitis, rhinitis, arthritis, and nephritis have also almost reached vanishing point, and it is quite an occasion in my fever class when I can show any one of these Perhaps with reference to the decline in the complications of scarlet fever one reservation ought to be made, and that is in respect of endocarditis Although never very common, at least during the period while the patient was under observation in hospital, this has not declined, and indeed in some years appears to have been on the increase With this possible exception it is clear that both epidemiological change and therapeutic advance have combined to deprive scarlet fever of its severity Whether this epidemiological change will be permanent is a question that no experienced epidemiologist will be likely to answer hastily All we do know is that scarlet fever provides the classical example of change of epidemic type which has altered certainly twice and probably three times within the limits of modern history

In diphtheria, with one important exception, there was little evidence of change of clinical type, and case fatality rates, though variable, remained over and sometimes well over, 5 per cent right up to 1942 The hæmorrhagic type had probably become less common, but the most striking change observed by those with much experience of the disease was the decline in incidence of the laryngeal form of the disease For example in 1903 Claude Ker noted that 50 per cent of the diphtheria deaths were due to laryngeal diphtheria By 1924 it accounted for 28 per cent , and in his annual report for 1935 Benson found occasion to comment on the virtual disappearance of laryngeal diphtheria However, this form of the disease, although much reduced, never entirely ceased to trouble us until the disease itself vanished Another feature of diphtheria in the first half of the century was the progressive shift in the incidence of diphtheria mortality from the pre-school to the school age This was not due to an alteration in the incidence of the disease but was the result of a proportionately smaller decline of the fatality in the 5-9 than in the 0-4 years age group I agree with those who attribute this alteration mainly to diminution in the average size of the family, and, if we accept this, we see how apparently unrelated social phenomena may initiate epidemiological change Perhaps at this point I may suggest that it is possible some very interesting epidemiological changes may occur as a result of the mass immunisation of the child population as there is some evidence that adult immunity, brought about in the past by sub-clinical infection, is on the wane If this is substantiated then we may expect diphtheria, should it be introduced, to become predominantly a disease of adults

With regard to measles I could not say with confidence that there has been much alteration in its clinical manifestations, or its complications, during the past thirty years, although we all know that the measles mortality has been steadily on the decline and that this has been definitely accelerated since the late thirties Since measles mortality was a pneumonia mortality to a great extent, I have no doubt in my own mind that this acceleration was in large measure due to the introduction of the sulphonamides Apart from mortality, measles has always been important on account of the chronic morbidity which often followed an attack Chronic otorrhœa for instance had become a serious public health problem and much of this could be attributed to measles in childhood Similarly with regard to visual defects, and, though Marshall and Seiler in 1942 reported that the specific fevers were a comparatively unimportant cause of blindness, of the small number of cases discovered in their survey three-quarters were due to measles Since penicillin became available eye and ear complications of measles have practically disappeared from our wards, and consequently as a source of chronic morbidity the disease should cease to be important Since the early twenties when interest in post-infective encephalitis was aroused by the investigations which pointed to post-vaccinal encephalitis as a direct sequel of vaccination, much has been written about its occurrence in measles, in which it is probably more frequently found than in the other common fevers Fortunately rare, this complication is a good example of what I have referred to as cyclical change in the characteristics of individual epidemic diseases, as it appears in some epidemics with greater relative frequency than others

Serious though whooping cough remains, and, from the point of view of treatment, still an unsolved problem, it is definitely on the wane as a killing disease, and the high hospital case fatalities of over 10 and even 20 per cent are no longer experienced In fact, although fortunately we have seen little of it in Scotland in modern times, the only disease which appears to have retained its capacity to reproduce its malignant type is variola major Observing the comparatively small number of cases which appeared in Edinburgh in 1942 we seemed to be translated to the clinical atmosphere of earlier days, confronted as we were by a disease which assumed a malignant form in about a quarter of the cases, and which evolved relentlessly to its fatal and loathsome conclusion without the slightest prospect of alleviation It is true that in the cerebrospinal fever epidemics of 1940 and 1941 the fulminating type was also relatively common but here we were not entirely helpless as even in this type sulphonamide treatment was not without its successes

As to the factors governing these qualitative changes in the common fevers these are undoubtedly complex, and discussions on their nature, and views as to whether they will continue to operate, would require a whole evening to themselves Our recent experience of poliomyelitis should teach us to be wary, and, while modern triumphs in prophylaxis and treatment of the acute infectious diseases may give us much cause for satisfaction, we should never forget that only the longest of long term views are permissible in epidemiology

A REVIEW OF INFECTIOUS DISEASES DURING THE FIRST HALF OF THIS CENTURY

CHANGING CONCEPTS IN THE COMMON FEVERS

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I HAVE thought that the purpose of this symposium might be best served if, instead of remaining completely factual in my outlook, I were to try to present to you a more philosophical background as it were , to attempt to portray the background upon which our modern view of infectious diseases is based My remarks may be conveniently divided under two headings—first, what might be called changes in the general principles underlying our attitude to infectious diseases , and, second, changes which have an important application in treatment of the patient in hospital or in the home

GENERAL PRINCIPLES OF THE BEHAVIOUR OF INFECTIOUS DISEASES

(*a*) *The Place of the Infectious Diseases Hospital in the Community* —There is little doubt that when the fever hospitals were first opened their sole purpose was regarded as preventive The principle was accepted that the isolation of infected persons in the infectious diseases hospital would remove from the community the source of infection and, in this way, eradicate the common fevers Although for a long time it has been appreciated that this cannot be carried out effectively, it is true to say that there remains a conception that the fever hospital's main purpose is the isolation of infected persons with a view to the saving of the remainder of the community Now there may have been something to say for such a view when the prevalent diseases were due mainly to dirt—typhus, typhoid and cholera, for example—but the vast improvement in civic hygiene which marked the end of the nineteenth century and the beginning of the present century itself caused a reduction in infectious diseases of this type During the present century more and more attention has had to be paid to the respiratory tract infections for the great majority of the common fevers of to-day are spread by the air Now, whereas the sterilisation of water and the separation of water from sewage, both of which measures so greatly reduced the prevalence of the bowel diseases, may be regarded as comparatively simple matters, the sterilisation of the air presents a much more serious problem When it is appreciated that many of the

Lecture given at a meeting of the Medico-Chirurgical Society of Edinburgh on 7th November 1951 respiratory tract infections are caused by organisms commonly present in the throats of healthy individuals, and when we realise that much of the time of any individual in the adult community is now spent in what might be termed crowds, either in travelling to or from his work, or while at his work (with a constant, consequent transference of organisms from one person to another), it becomes obvious that the number of infected persons outside of the fever hospital greatly exceeds that in it Now I can almost hear you say " Surely you are not advocating a policy that the infectious diseases do not require to be admitted to hospital at all " It is important in this respect to make a distinction between what might be called " endemic " and " exotic " infections The endemic infection which is constantly present in the community frequently gives rise to minimal attacks so that there is a wide variation in the severity of infectious disease which results—much of it escaping recognition The " exotic " infection, on the other hand, which is rarely present in the community tends to produce a much more obvious form of the disease, so that practically all the cases are readily diagnosed and admitted to hospital Since very few members of the community have had experience of these exotic infections it is a matter of public health importance to achieve early diagnosis and early segregation in the fever hospital, for then the foci of infection are greatly reduced in number The fever hospital, therefore, like any other specialist hospital exists nowadays mainly as a place in which expert medical and nursing attention may be given to severe forms of acute infective disease and only to a small extent as an isolation unit for unusual epidemics For many of the common infections it would be a waste of hospital beds to suggest that all cases be removed to hospital, and most public health departments now carry out a policy which ensures that patients receive hospital care either by reason of the severity of their illness or because social conditions make it imperative that the patient should receive more adequate attention Fortunately, it is true to say that the treatment of most infectious diseases can be adequately carried out in the home provided a few simple precautions are taken

(*b*) *Infectious Diseases as a Problem in Biology* —For long into the present century there is little doubt that almost the sole emphasis in infectious diseases was placed on the pathogen No doubt this was largely motivated by the early work done by the bacteriologists in ascribing to certain diseases certain parasites As a result, we regarded certain infectious diseases as being " caused " by certain organisms, the underlying implication being that all the clinical manifestations of infection were produced by the organism In recent years we have tended to move away from this concept and to emphasise more and more that the host plays a large part in deciding the pattern of the infectious disease This question of host-parasite relationship is undoubtedly a very important one and it may be conveniently dealt with under three broad groupings first, on the mass scale , second, on the individual scale, and third, on the cellular scale So far as the mass scale or the community is concerned there is no doubt that the behaviour of the community imposes itself upon the pattern of infectious diseases prevalent in the community Two examples may suffice to make my point Up to the beginning of the recent war, one of the important claims made by the hygienist was that the improvement in public sanitation and in personal hygiene had resulted in the virtual disappearance of the bowel diseases from this country—dysentery was uncommon and typhoid only reared its head on occasions with small epidemics During the last eight or ten years, however, dysentery and food poisoning have become almost the most common infections prevalent in the British Isles What has occasioned this change ? Is it the appearance of new organisms ? Is it the development by old organisms of new capacities to attack the human host ? It seems very unlikely that the explanation lies in anything to do with the parasite It seems much more probable that the occurrence of strict rationing at the beginning of the war which resulted in the opening up of new restaurants often in premises quite inadequate for such purposes—the encouragement given to school canteens and work canteens to supply mid-day meals—the shortage of foods which resorted in the reheating of leftovers, and the development of the transport industry with its mass of men moving about the country from one place to another and eating in small unhygienic restaurants in small villages—all of these combined to change the community from one where all fed at home to one where everyone was taking some meals outside It seems likely that this change has exposed man to risks entirely novel to him Far from the organisms having increased in virulence or in attacking power, it is probably true to say that the very mildness of the illness produced by most of them is itself important in that it encourages the individual to remain at work when he is suffering from the disease with the result that any fault in hygiene results in a greatly increased spread of infection Or, to take another example, the so-called gastro-enteritis of infancy—there is no doubt that this disease was very prevalent at the beginning of the century Recurring epidemics, usually in the summer time, took a large toll of child life Then in the 1925 period with the disappearance of horse traffic and its replacement by motor traffic, the disease almost disappeared There can be little doubt that the high prevalence of this infection in the early 1900s was largely due to contamination by flies Then, in the late 1930s, the disease reared its head again This sudden reapperance was not always associated with summer epidemics On some occasions the outbreak occurred during the winter Association with flies could rarely be proved Indeed, the careful examination of these cases often failed to reveal any evidence of infection and pathogenic organisms could not be isolated from the stool The one feature which was common to nearly all epidemics, however, was that breast-fed babies usually escaped, whereas bottle-fed babies were much more susceptible to attack Much work yet remains to be done on this condition but, in my view, the ultimate cause lies in some fault of nutrition which results from bottle feeding so that resistance to all types of infection is reduced These two examples will suffice, although others could be given to indicate that the pattern of infectious diseases prevalent in any community is not merely decided by the kind of prevalent organisms but by the behaviour of the hosts in a community

When we come to the individual the same general principle may be applied All hosts are not the same in their make-up There is great inequality in their capacity to resist infection As a result, all types of clinical manifestation may be recognised when the infectious disease is prevalent in the community Epidemics due to the meningococcus form an excellent example of the variation in response to the same pathogen by different hosts Our modern view of a meningococcal epidemic would be that by far the great majority of the populace become mere carriers of the organism, either for short or long periods There is, it might be postulated, a naso-pharyngeal barrier to the passage of the organism into the tissues of the host so that the epidemic is, as it were, an epidemic of carriers In a few individuals whose resistance has been lowered (and it is probably some precedent lowering of the cellular state of resistance of the nasopharynx that is responsible) the organism, having penetrated the nasopharynx, enters the bloodstream and rapidly penetrates the blood brain barrier to produce meningitis In the great majority of these cases the organism merely stays in the bloodstream for a very short period and produces little or no damage during transit But, in a very small number of persons, the entry of the meningococcus into the bloodstream is followed by the most widespread damage and an acute fulminating septicæmia results—an illness which may kill the patient in a matter of a few hours Here again we see that it is not any undue virulence on the part of the organism which causes this variety in the clinical pattern of disease, but the interplay between parasite and host which produces in one person a carrier state, in another meningitis, and in another a virulent septicæmia

But the picture of host-parasite relationship must eventually be taken down to the smallest scale, namely, to the cell and here one must understand the difference between the bacterium and the virus as a cause of infection One of the profound differences between them is that the former is an extracellular parasite existing in the intercellular spaces, whereas the latter is an intracellular parasite, breeding inside the walls of the cell itself Now although this point is appreciated by most clinicians, few have taken it to its ultimate interpretation So long as the attacking parasite remains outside of the cell, it is obvious that treatment will be a comparatively simple matter Any substance which enters the bloodstream and passes from the blood vessel into the tissue fluids will reach the organism and, with our modern forms of chemotherapy, may be expected to subject it Virus infections, on the other hand, present an entirely different problem Here, when there is clinical manifestation of disease it may be accepted that the virus is already inside the cells As a consequence, two conclusions are reasonable First, any therapy which is going to kill the virus must almost certainly kill the cell as well , and secondly, virus damage will, as a rule, result in cellular damage and, in some tissues the replacement of important cells destroyed by virus may be impossible The introduction of powerful chemotherapeutic agents has induced the concept in our minds that all infectious disease will ultimately prove amenable to treatment, but it needs to be emphasised that the diseases which so far have proved susceptible to chemotherapy are practically all bacterial diseases The only near-virus diseases which we have been able to treat are the typhus group of fevers, where the rickettsiæ not only exist intracellularly but also show periods of invasion of the bloodstream I think it is true to say that there is no real evidence that true virus infections of a systemic character have yet proved susceptible to chemotherapy

(*c*) *The Importance of Social Conditions* —All of the early epidemiologists laid great stress on the environmental background of the infectious diseases There can be no doubt of the importance of social conditions in the spread of infectious diseases But two aspects of social conditions which have not perhaps been given the emphasis that they should have received are nutrition and family size My experience would suggest that the most striking change that has occurred in the last twenty years is in the nutrition of children admitted to hospital The greatly increased neonatal and child welfare supervision, the supply of milk to schools and school meals, all of these have played an important part in increasing the resistance of the host to bacterial infection and have an important bearing on the reduction in the severity of infectious diseases We are often misguided enough to believe that the reduction in severity is entirely due to chemotherapy and we need to be reminded that the infectious diseases had been improving in this respect, long before chemotherapy was introduced An analysis of the figures in Glasgow shows that mortality from pneumonia for example had fallen greatly in the ten years 1920-1930 The freedom of the population from serious infectious disease during the war was probably due to the wise feeding policy that was adopted Nevertheless, improved nutrition and the rapid subjection of bacterial infection produced by modern chemotherapy may carry certain dangers The importance of realising the difference between bacterial and virus attack has been emphasised Although it is reasonable to argue that a well nourished host may be the better able to withstand bacterial attack it might also be argued that if the virus is dependent upon the nutritional metabolism of the cell then it may be that a cell which is actively metabolic and well nourished is preferred by the virus Such a concept is not an entirely novel one We have long known that the rash of smallpox, for example, prefers the exposed parts of the body We say that the rash appears on the traumatized skin. Is it not possible the virus prefers these sites because the cells are there very active and in continual replacement. As a more recent example poliomyelitis might be cited. It might be suggested that the increased prevalence of poliomyelitis in the last few years may be due to the enhanced nutrition of the cells of the body which encourages the invasion of the poliomyelitis virus. But if this seems rather a tenuous argument to put forward, there can be little doubt that the virus prefers central nervous system cells which are in a state of activity, and Ritchie Russell has shown that excessive muscular activity may play an important role in initiating severe paralysis. It is easy to think of this as indicating that a tired muscle is more likely to become paralysed but it seems possible that the virus parazitizes a cell which is in a state of great activity and therefore able to produce the kind of feeding material which the virus prefers.

In regard to the size of family little work has been done in trying to correlate the reduction in severity of infectious diseases with the reduction in the size of family. But it may be that one of the important factors which has reduced the severity of such conditions as measles in the last twenty years is smallness of the modern family. With a large family the presence of measles in the household (introduced so often from school) resulted in the infection of a considerable number of younger siblings. Nowadays, it is not uncommon to find that the older member of the family has passed through the common infectious diseases before the newcomer arrives. This has the effect of raising the age of attack and, as a result, the severity of the illness is reduced.

CHANGES IN THE MANAGEMENT OF THE DISEASES

(*a*) *The Importance of Cross-Infection.*—It may come as a surprise that I would regard our increased knowledge of the means of cross infection as perhaps the most important advance in knowledge that has taken place in recent years. At the beginning of the century and well into the 1920s the concept was generally held that infectious diseases were spread by droplet infection. It is true that in the case of smallpox and chickenpox some attention was paid to what was termed aerial transfer but the mode whereby aerial transfer took place was not at all clear. Mainly as a result of the work undertaken by Cruickshank in Glasgow and by the Wells in the United States of America it soon became apparent in the 1930s that infection could be spread by a variety of means—principally, by the air and by the dust. It was appreciated that the moist droplets, in their descent through the air, became reduced in size by drying and that by these much smaller "droplet nuclei" infectious material could remain suspended in the air to be carried by draughts considerable distances, or might settle on bedclothes or on the dust of the floor to be raised during bedmaking and the domestic sweeping. Had it not been for the war this would have had a profound effect upon fever hospital design, for it is obvious that to congregate infectious diseases in large numbers in open wards, as was the practice in the past, enhances the risk of cross-infection Ward units in fever hospitals should be small and not contain more than four to six persons Further the method of nursing should demand greater attention to personal hygiene so that the transference of infected material from patient to patient is reduced to the minimum One might indeed go so far as to say that the occurrence of certain complications forms an excellent index of the efficiency of the management of a hospital for infectious diseases Thus, otitis media is recognised as a complication of scarlet fever, but there is no doubt that a considerable proportion of such cases develop this complication not as a result of the original infection but because the patient acquires another organism from his neighbours when he is convalescing from the original attack It is thus possible to say that if an otitis media develops in the first week of scarlet fever it is likely to be a complication of the original infection, but that when it occurs thereafter it is much more likely to be due to cross-infection from some other member in the ward Such a view is of great importance for it follows that if the cases are properly managed the incidence of the complication may be reduced very considerably Dr W T Benson enunciated the view that when a measles ward received more than a quarter of its complement with a broncho-pneumonia present on admission, then cases admitted to that ward without broncho-pneumonia were very liable to contract it This knowledge of cross-infection is of the very greatest importance in children's wards in no matter what type of hospital and the necessity to take strong measures to avoid cross-infection in burns and plastic surgery units has, of course, already been widely appreciated

(*b*) *Chemotherapy*—Little need be said about the progress of chemotherapy in the last fifteen years Most of us will agree that our change in outlook in regard to treatment has been profound During the period 1900-1935 the accepted view was that the correct treatment of an infectious disease involved first, finding its cause, and then second, producing an antiserum in some larger animal However, apart from diphtheria, scarlet fever and tetanus, the use of antitoxins and antisera have now little place in treatment Nevertheless, as we progress from one antibiotic to another, it is perhaps worth recalling the great advance which was made with the introduction of sulphonamides in 1935 It might not be too much of an exaggeration to say that the sulphonamides played a more important role than penicillin in the recent war The vast epidemic of meningococcal infections which marked the outbreak of the war would have had a disastrous effect on life—and on morale—if we had not possessed an effective form of therapy which reduced the mortality to between 10 and 15 per cent The widespread prevalence of dysentery in the Middle East during 1942 was effectively controlled by sulphonamide and the part played by these chemicals in restoring troops to the field more rapidly was immense

But the story has advanced greatly since those earlier days We now have a chemotherapeutic material capable of attacking almost every bacterial disease When one method fails, another can step forward to take its place Whooping cough alone remains amongst the infectious diseases as still resistant to chemotherapy The list of the victories is a most impressive one, the sulphonamides with their great activity against meningococcus infections, pneumonia, urinary infections and the dysentery group, penicillin effective against staphylococcal, and pneumococcal infections, streptomycin and its efficacy in some forms of tuberculosis and finally, chloramphenicol and aureomycin with their wider range of activity bringing enteric fever and typhus under control

(*c*) *Secondary Effects of Chemotherapy* —The materials are now in our possession which profoundly affect bacterial life If bacteria were only to be found in the human body during infection then of course to kill them would always be a good thing But we all carry in our nose, throat and bowel a microflora which, it would not be too fanciful to suggest, is of the greatest importance for our health Now the administration of chloramphenicol to a patient means in effect that we sterilise his nose and throat in a matter of six to twenty-four hours and kill a high proportion of the organisms in his intestinal tract in a matter of two to three days Such a change is an unnatural one and since nature seems to dislike a vacuum it is not an unnatural effect of this change that other bacteria should enter to take the place of those that have left Under such treatment the predominant fæcal flora may become fungal Thus, although fungi can be grown infrequently from the fæces of pneumonia patients on admission to hospital, they are an almost invariable finding after four or five days' treatment with an antibiotic of the nature of terramycin In many cases the sputum produces a considerable growth of monilia In this country where these antibiotics are still on short supply and are very expensive such changes produced have not been great in magnitude, but in America the changes in the flora of the throat have already become considerable and deaths from monilia infection have actually occurred I would be so bold as to prophesy that the increasing and widespread use of these powerful antibiotic agents may produce profound changes in the host and that this will, in time, show itself in a changing pattern of infectious diseases

It is perhaps of interest to draw your attention to another aspect of biological relationships You will recall that during the war the introduction of D D T was heralded as a major advance The application of D D T to the prevention of typhus fever made a great contribution to the Italian campaign And yet to-day, within ten years of the introduction of D D T, we find that flies are developing resistance to it and that in certain regions the prevalent form of fly is now completely resistant to the action of D D T Further, and of very great interest, it has been found that individuals in towns who have had no known contact with D D T whatsoever yet may show the presence of D D T in their blood, presumably resulting from the ingestion of fruits and other materials which have been sprayed with D D T Our duty as doctors seems clear—we must attempt to prevent and, when not preventable, to treat successfully all acute infections It is well that we should constantly remind ourselves that in so doing we are interfering with a biological relationship Such interference cannot be undertaken lightly Bacteria and viruses, like the poor, will be ever with us When the host-parasite relationship is simple (as in the case of diphtheria) a very simple mechanism may induce complete immunity in the host But where, as in the majority of infections, the host-parasite relationship is complicated then we are unlikely to interfere with impunity The parasites will tend, in time, to find a method of circumventing our form of interference The newest antibiotics place in our hands the means of making profound changes in the microbiology of man Let us see that we use them with thoughtfulness

Discussion

Colonel Morison, opening the discussion, recalled that in 1905 he was in charge of fever wards in a London Hospital and on his return from India in 1920, he was shown over them by his old chief, who reminded him that, while in 1905 toxic scarlet fevers were very common, they were rarely seen now

Another point he was interested in was Dr Anderson's reference to the fall of infantile enteritis after 1910 being due to the disappearance of horses Colonel Morison thought that in London it was much more likely to have been caused by the chlorination of the water supply introduced by Sir Alexander Houston He had noticed this occurring in India

Dr Douglas Robertson thought that scarlet fever was the outstanding instance of a disease which had varied in intensity from time to time Eighty years ago it was a dangerous killing disease, whereas now it was almost trivial We had no convincing theory to account for this variation in severity He considered it anomalous that a case of streptococcal tonsilitis with a rash should be isolated in hospital, while an equally infectious case without a rash was kept at home

Although whooping cough was regarded as one of the most fatal diseases in children under five, this had not been his experience Possibly he had been fortunate

Dr Robertson was disappointed that the most deadly of all infectious diseases in this country had not been mentioned—tuberculosis Patients with scarlet fever were rushed off to hospital, while young children were still allowed to remain in close contact with tuberculosis under shocking housing conditions It was a tragedy that we were still seeing cases of tuberculous meningitis almost certainly due to direct infection from near relatives in the home It was our duty, as medical men and women to do all we could to arouse the conscience of the nation and of our health and housing authorities to look upon tuberculosis as the gravest public-health problem facing us to-day, and to take decisive action with a sense of urgency

Dr A Fergus Hewat said that he had had a good deal to do with cerebrospinal fever during the 1914-18 war, and had been struck by the wonderful recovery rate resulting from serum intrathecal injections

Dr Hewat had at one time been in charge of a boys' school for a year and had to look into the subject of fevers at that time He had been particularly interested in the introduction in Dr Claude Ker's book on Fevers published in 1909 to the subject of smallpox, which ran as follows —" It is a subject for legitimate regret that a textbook on fevers, written a century after the introduction of vaccination, should still have to include an account of a disease which should long ago have been classed with such conditions as the ' Sweating Sickness,' or the ' Black Death,' and relegated rather to historical treatises It is an interesting and curious comment on our boasted civilization that, with the means of absolutely preventing smallpox at our disposal, we allow the prejudices of a small minority to still expose the country to not infrequent outbreaks of a peculiarly repulsive and filthy disease But unfortunately, so long as vaccination and re-vaccination cannot be universally enforced, smallpox will continue to be with us, and, unfortunately also, will continue to be the cause of most regrettable loss of life and waste of money "

Also quoting from the same book (p 183) there was an interesting paragraph on the value of vaccination —" The admirable results obtained by systematic *re-vaccination* are perhaps the most striking proof of the protection which can be secured if full advantage is taken of Jenner's discovery In Germany, since re-vaccination has been enforced, smallpox has been almost unknown. The few individuals who contract it are for the most part foreigners who have not been re-vaccinated " " Contrast Berlin, with its 12 beds for smallpox in a pavilion of a general hospital, with London, with its 2500 beds in hospitals specially constructed and maintained for smallpox alone The German law insists on re-vaccination at school age and the male adult population is again re-vaccinated on entering the Army " Dr Hewat asked what was the present position in regard to smallpox

Dr Hewat expressed the cordial thanks of the meeting to the two speakers for their most interesting and instructive papers

Dr Joe, in reply, said he had not much to add, but he too had received great stimulus from Dr Anderson's paper

With regard to the chlorination of water, Dr Joe drew attention to the fact that the Edinburgh water supply was not chlorinated until the outbreak of war in 1939 but hospital admissions for bacillary dysentery continued to rise until 1944 and 1945

Scarlet fever, Dr Joe pointed out in reply to Dr Robertson, is not merely streptococcal tonsilitis with a rash The rash is not unimportant as it is the expression of a specific generalised toxæmia, which, in the malignant form of the disease, can kill the patient

Tuberculosis had not been touched on as he had understood his remarks were to be confined to the acute fevers However, as far as hospital treatment was concerned, lack of nursing staff was largely at the root of the trouble and failure to recruit nurses was due to fear of infection Until this difficulty could be overcome and defective provision of housing remedied the disease would remain a problem

Dr Anderson, replying, said he was interested to hear Dr Brownlee's name mentioned—his laboratory at Ruchill was called the Brownlee Laboratory

Dr Anderson regretted the omission of tuberculosis but he understood that " The Common Fevers " was the subject under discussion He agreed heartily with Dr Robertson's remarks During the summer he had arranged a conference in Copenhagen and had been impressed once again by the Danish attitude to tuberculosis One never saw a case of tuberculous meningitis in children He quoted the case of Dr H C A Lassen who started with 100 beds set aside for the treatment of children with tuberculous Since 1935 the numbers had gradually fallen until he had only 14 beds occupied Until this country became as conscious of the disease as the Danish medical profession and general public, we could hope for little improvement

HÆMATEMESIS AND MELÆNA

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INTRODUCTION

IN opening the discussion on hæmatemesis and melæna, I at once feel envious of Mr Samuel Pickwick His observations on Tittlebats and the Source of the Hampstead Ponds so unfortunately omitted from the text of the *Posthumous Papers*, must have struck an original note even when delivered before the famous Club he founded In sharp contrast, our Society meets to discuss a condition upon which each member, well informed and wise by the teaching of slow experience, can express opinion and find himself in general agreement upon principle and in dispute only on matter of detail Not assembled to register some massive development in medical science, we are met to record the changed state of mind that now stands revealed in us who have held in our hands the unpredictable fortunes of our fellow-men suffering from hæmorrhage high in the alimentary tract It is a sobering fact that in spite of our new thoughts and methods, barely five more lives are now saved in every 100 cases when comparison is made with the older statistics

Our purpose is well served if the term hæmatemesis is confined to the vomiting of blood in moderate or greater amount, and melæna to the passage of black, tarry stools

CASE MATERIAL

The anatomy and pathological background of this condition is well illustrated by reference to the records obtained by autopsy upon 145 cases who succumbed to hæmatemesis and melæna in Edinburgh Royal Infirmary during the years 1940-49 Although a slight increase in numbers can be discerned during the last five years of this period, merry War and disgruntled Peace have each failed to make significant change in the autopsy rate for this disorder in Edinburgh, a city so remarkably free from the anxieties of aerial attack Figures culled from such a source fail to give accurate impression of a disability from which most patients recover Study has therefore been additionally made of the clinical records of 145 patients suffering from hæmatemesis or melæna who have come under personal observation during the last five years The diagnosis in this series is based upon the clinical manifestations, aided by biochemical and radiographic evidence, supported in some

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Read at a meeting of the Medico-Chirurgical Society of Edinburgh on 2nd May 1951 cases by gastroscopy and in other instances by operation or ultimate autopsy (Table I)

In common with other published tables, the figures in each series fail to give satisfaction Listing only a disease process causing hæmorrhage, the table is not only inadequate, for mention is not made of other disease contributing to the hæmorrhage or ultimate issue, but also inaccurate for detail is lacking of the multiple ulceration commonly found in the gastro-duodenal area For example, one patient with hepatic cirrhosis died of hæmorrhage caused by a large gastric ulcer penetrating varices extending from the œsophagus to the lesser curvature A further case who survived operative repair of a perforated anterior wall duodenal ulcer succumbed within a few days to severe hæmatemesis and peritonitis Of 7 other ulcers demonstrated in the gastro-duodenal area at autopsy, 2 had been the seat of hæmorrhage and 2 of recent perforation, each of these catastrophes affecting ulcers in the stomach and in the duodenum

TABLE I

Diseases	Autopsies (1940 1949)	Ward Cases (1946 1950)
Hæmatemesis and/or melæna	145 (of 5409 cases)	145
Melæna neonatorum		1
Foreign body in œsophagus		1
Cirrhosis of the liver	16 (of 84 cases)	1
Portal vein tumour	1	
Œsophageal hiatus hernia—		
with gastric ulcer	1	
with duodenal ulcer		1
Peptic ulcer—		
of œsophagus		2
of stomach	50	28
of duodenum	55	67
Anastomotic	3	5
Acute erosive gastritis	3	
Diverticulum of stomach		1
of duodenum	1	
Benign tumour of stomach		1
Carcinoma of stomach	10 (of 113 cases)	2
Carcinoma of pancreas	1	
No cause demonstrable	4	35

Good pathological records make fascinating reading and every clinician has his day made happier by some laudable correct diagnosis In almost every instance in the present series where the pathologist demonstrated bedside opinion at fault, the cause of the error could be found in one of those factors well-known in practice which make defeat and not disgrace the outcome of careful clinical effort

Elaboration of the figures provided in Table I would appear desirable only in respect of those in the necropsy series relating to peptic ulcer Of the 50 cases of gastric ulcer, 32 were male subjects In 30 patients the lesion was situated at the middle of the lesser curvature, and in the remainder in the prepyloric region, with the exception of 2 cases who had involvement of the lesser curvature near the cardia The solitary instance of benign ulcer of the greater curvature occurred in a patient who died of hæmorrhage from one of two ulcers on the lesser curvature Of the 55 cases of duodenal ulcer, 45 were males and the disease was found on the posterior wall either alone or with associated involvement of the superior or inferior aspects in all except 12 cases in whom there was anterior wall ulceration More than one bleeding point could be demonstrated with the naked eye in the floor of the ulcer in 17 gastric and 8 duodenal cases Multiple ulceration of the stomach was found on 5 occasions, of the duodenum in 9 instances and in a further 9 patients in both the stomach and the duodenum

Although this necropsy series refers only to patients dying of hæmatemesis or melæna, it is of interest for comparison to note that in the autopsy records of perforated peptic ulcer over the same period, this complication affected a greater number of individuals with higher incidence amongst males and more frequent involvement of the duodenum, and caused the greatest mortality in the sixth and seventh decades Surgery was employed in almost every instance

THE SOURCE OF THE BLEEDING

Emphasis must be placed at once upon the simple but inescapable fact that all blood lost by hæmatemesis or melæna has a point of origin in relation to the alimentary tract

Jolted by each new fact or concept in relation to the vascular mechanisms of the gut, the observer experiences a certain relief in the static character of the anatomy of the vessels which are potential sources of hæmorrhage Above the diaphragm the aorta leaks or bursts into the trachea rather than into the œsophagus The vena azygos was the site of hæmorrhage in a child included in the clinical series who had swallowed a halfpenny one year previously Lodged in the long axis of the œsophagus, the coin had not caused complaint until the terminal erosion of this large vein Well remembered but infrequently encountered, bleeding the result of peptic ulceration or portal hypertension occurs from the intra-mural vessels at the lower end of the œsophagus Below the diaphragm, aloof and removed from injury, the aorta and inferior vena cava each run their separate course Equally remote from danger the main stems of the aorta provide the last specifically named branches which by their position and size are the occasional source of fatal exsanguinating hæmorrhage At point of greatest risk within the wall of the gut, in the substance of the pancreas or in close relationship to these structures run the small vessels, nameless and innumerable, which are the common source of bleeding of any degree of severity In size capable of admitting the point of a lead pencil and in number usually one and not more than three, the damaged vessels are commonly as easily discernible as the disease responsible for their rupture Yet in 4 cases of massive hæmorrhage upon whom autopsy was performed within twenty-four hours of death, causative pathology and bleeding point were alike in their conspicuous absence

Cause and effect are well seen when bleeding point and focus of pathology occur in association with a gut full of blood Even in the absence of such bleeding point the disease with good reason may be held responsible for the hæmorrhage Fourteen cases in the series of peptic ulcer did not exhibit point of bleeding at autopsy In a recent series of 66 cases of hepatic cirrhosis previously reviewed, 9 of 18 cases dying of hæmatemesis failed to show the customary small laceration overlying the œsophageal varix Notorious as camouflage, autolytic change and retraction of bleeding point mask the presence of pathology, notably acute ulcer with erosion of arteriole The very acuteness of the lesion may lead the surgeon astray In each of 2 cases of my series an acute duodenal ulcer with bleeding point was found at autopsy, having been missed at laparotomy a few hours previously

The large number of 35 cases in the clinical series in whom the cause of the hæmorrhage was never discovered is in accord with general clinical experience None of these patients died None suffered from hæmorrhage of sufficient degree to warrant operation None was subjected to gastroscopy, a procedure of recognised limitations Thus two opportunities for obtaining accurate direct information never presented The third method was never employed Making comparison with other similar cases in whom diagnosis was established, study of this series suggests that at least 18 of the number suffered from acute ulceration in the gastro-duodenal area Chronic peptic ulcer was responsible for the remainder with the possible exception of a single case in whom a less common cause for hæmatemesis might ultimately be discovered

FACTORS PRECIPITATING THE HÆMORRHAGE

Out of sight yet strangely responsive to a wide variety of influences, the alimentary tract fails to provide in the healthy subject indication of constant activity Although assessment of motor and secretory function of the gastro-duodenal area may be made with a degree of accuracy sufficient for clinical purposes, there does not appear to be at present any method readily available to define the varying blood flow and vascular mechanisms in this important region With superficial and deep network in the mucous membrane linked with a plexus in the submucous and in the muscular coats, an arrangement affording admirable exposure to injury, the blood vessels show constant alteration in calibre under nervous and biochemical influence Local demands from the gut add to the burdens already laid by the stresses and strains of the general circulation Brooding over the whole area is the unquiet and troubled brain Contending with the fretful elements of the mind, the blood ripples through the vessels with each light breeze or squall or surges against its containing walls with every storm that blows Assailed by all these forces, the stomach and duodenum exhibit a resilience and resistance to hæmorrhage that is at once truly remarkable and hitherto inadequately explained

Commonly unheralded, the long arm of Fate stretches out Events which yesterday passed without incident today cause hæmorrhage of any degree of severity In the clinical series of cases of peptic ulcer, 30 patients reported a usual exacerbation for unknown reason of dyspepsia a few days before their hæmorrhage Fifteen cases suffered from psychiatric upset freely admitted An equal number described in the few days preceding the bleeding a short period of general malaise, sometimes attended by coryzal symptoms Nine cases had indulged in dietetic indiscretion and 5 in strenuous exercise Yet a further 3 had the hæmorrhage shortly after rising in the morning One patient reported the uncomplicated extraction of many carious teeth the day before his hæmatemesis

Whatever the effect of these naturally occurring events, the gastroduodenal area resents surgical interference Five patients after gastroenterostomy suffered hæmatemesis from one or more peptic ulcers demonstrated at autopsy, when additional perforation was found in 3 of these cases Three patients after operative repair of perforation had bleeding from an adjacent ulcer In 3 cases of fatal hæmorrhage after partial gastrectomy, the pathologist demonstrated bleeding from an infected hæmatoma in one individual, from mucosal lacerations along the line of the clamps in another, but in the third, the source of hæmorrhage could not be defined Even when surgery is conducted away from the alimentary tract bleeding may occur from an area of new ulceration or a previously existing ulcer One patient died of hæmatemesis following inguinal herniotomy, and in 2 cases subjected to pelvic floor repair, death resulted from hæmorrhage from a gastric ulcer in the one subject and in the other from multiple superficial gastric erosions The small number of fatal cases viewed against the large number of operations conducted upon healthy and ulcer subjects shows that the risk, although present, is in no way severe

Previous attack of hæmatemesis has little effect upon mortality or incidence of recurrence Throughout the series only one case in every 4 gave the story of antecedent bleeding from the stomach or duodenum

THE RESULT OF THE BLEEDING

Survey of the varied pathology renders obvious the fact that a satisfactory result cannot always be attained Even in the absence of mortal disease and of exsanguinating hæmorrhage, the loss of blood may ruin the economy of a body already strained by advancing years or progressive disease commonly of cardio-vascular origin

Without flurry or fuss, 93 patients (67 per cent) in the clinical series of proved and probable peptic ulceration made uninterrupted recovery Except in few instances in this group, the hæmoglobin level, rightly accepted as inaccurate guide, never fell below 50 per cent , a figure in keeping with the clinical assessment of each case In the remaining 45 patients (33 per cent), the hæmorrhage was severe with hæmoglobin levels ranging between 20 and 40 per cent Each case was given transfusion of varying amount of blood and 11 were subjected to operation A total of 13 patients died Poised on the very confine of Nature and broken by cerebral vascular accident, prostatism or advanced cardio-respiratory disease, 5 old men tumbled into their graves One younger man after perforation of a duodenal ulcer and 3 subsequent severe hæmorrhages died shortly after admission to hospital Two men over the age of 70 years succumbed with continued bleeding, the one refusing operation and the other dying during transfusion Two males in the sixth decade failed to survive persistent bleeding on conservative treatment Of the 3 fatalities following operation, all were middle-aged and had previously shown poor response to transfusion Autopsy failed to reveal obvious cause for death

TABLE II

Mortality—Peptic Ulcer Group

Age Incidence	Autopsy Series	Clinical Series
10 19		(4)
20 29		(11)
30 39	11	(22)
40 49	16	1 (22)
50 59	23	5 (24)
60 69	34	2 (11)
70 and over	25	5 (9)

Figures in brackets indicate total number of patients in each age group

Ever dramatic, massive hæmorrhage becomes sinister in the absence of manifest bleeding Two patients with peptic ulcer in the autopsy series died within minutes of the onset of their symptoms of acute anæmia without visible hæmatemesis or melæna, yet at necropsy the intestine was loaded with blood A further short series of patients died within the hour of arrival at hospital, having sustained a severe hæmorrhage a short time before admission In all these instances, the cause of death must be associated with the sudden loss of much blood Less obvious is the reason for fatal issue in those patients who bleed continuously or intermittently at slower rate over longer period and in those who fail to survive operation without demonstrable cause In presence of marked anæmia, related anoxia and varying degree of sustained hypotension, the cells of the body suffer injury proportional to their circulatory requirements A single factor cannot be incriminated in the human subject whose metabolism exhibits considerable stability even under adverse circumstances Whatever conclusions are drawn from the results of experimental work suggesting the liver to be at fault, a small series of my cases of hæmatemesis failed to show disturbance in hepatic function when subjected to liver efficiency tests commonly employed in clinical practice The effect of hæmatemesis upon patients with chronic liver disease is well known Barely one-third of the patients dying with this symptom in my series of cases of hepatic cirrhosis succumbed to their first attack, the others surviving for periods often longer than two years, during which time inexorably there occurred further hæmorrhages and progressive injury to the liver parenchyma Above all, the human subject is not always fashioned in the same mould, and showing varying degrees of pathological change elsewhere, he cannot show a constant response to hæmorrhage Throughout the clinical series, the fatal cases were not those who sustained the most severe hæmorrhage or maintained for longest time the lowest blood pressure

OBSERVATIONS UPON MANAGEMENT

Hæmatemesis is merely an incident in the course of some pathological process the recognition of which in the living subject must frequently await the outcome of successful treatment Although assistance in diagnosis is often obtained from the clinical history, physical signs of causative pathology notably in peptic ulcer are commonly absent In 18 cases dying of hæmatemesis in my series of hepatic cirrhosis, 9 showed splenomegaly of which number only 2 had palpable enlargment of the liver

The patient rapidly exsanguinated by continuing massive hæmorrhage is without hope of relief The case in whom spontaneous arrest of bleeding is soon forthcoming will get better even in the absence of skilled attention Between these two extremes and outstanding as thereapeutic emergencies are the patients with interrupted or continuing hæmorrhage, and those ill cases in whom after loss of much blood there is doubt if the bleeding has ceased In all such instances transfusion is required not only to replace blood lost but to assist in the arrest of hæmorrhage Ancillary to this procedure are rest, sedation and a dietary in accord with the suggestions of Nature and thus the wishes of the patient, rather than in line with the dictates of Lenhartz or Meulengracht As the blood drips into the patient, at slower rate and in less amount in the elderly subject, a respite is gained giving time to reflect upon the employment of surgery or further conservative treatment The bulk of the patients recover on medical measures alone

Dismissal of those cases in the autopsy series in whom the uncomplicated pathology alone ensured a short expectation of life, permits of concentration on the patients dying of hæmatemesis the result of peptic ulceration Surely in the younger age groups some of these people could have been saved Glaring up from the records are three outstanding faults—inadequate transfusion, procrastination and infirmity of purpose on part of physician and surgeon alike, and ineffective operative method To be too niggardly in the giving of blood is certainly a worse sin than to continue transfusion after there is every indication for operation Very few pints are necessary before the response of the patient permits of decision concerning further management Operation may give the only chance of survival to the subject with continued bleeding and poor response to conservative treatment Remarkably far from the truth is the statement heard after effort at resuscitation that the condition of the patient is too bad to allow of operation. Although some minor operative procedure or even the mere handling of the stomach or duodenum, may be sufficient to arrest hæmorrhage, the surest method would appear to be partial gastrectomy Loss of life in bleeding peptic ulcer can only be excused in the presence of advanced age, of serious disease elsewhere or of continued hæmorrhage without facility for adequate treatment Whatever the many views expressed upon the indications for operation in this disorder, the competent physician must accept in practice the principle that when his clinical judgment informs him his patient is not making the progress he would wish on account of hæmorrhage the time has come to demand surgery

My thanks are due to the Pathologists of the Royal Infirmary, Edinburgh, for access to their case records and to Professor D M Lyon for permission to include in the clinical series cases observed in his charge

HÆMATEMESIS AND MELÆNA

By W A D ADAMSON, M B , F R C S Ed
Assistant Surgeon, Royal Infirmary, Edinburgh Surgeon, The Deaconess Hospital, Edinburgh

THE role of the surgeon in the treatment of hæmorrhage from a peptic ulcer is essentially a minor one As Dr Batty has shown only 5 per cent of such cases are likely to die While the surgeon, by operating on all cases of hæmorrhage, may obtain a mortality rate as low as 5 per cent , I feel that his essential function is to attempt to save, by surgical measures, some of the 5 per cent that would otherwise die My aim has therefore been to try to select those cases where surgery may be life-saving, and the more careful the selection the greater will be the service rendered and the fewer the operations

I will speak this evening only of my own personal experience of the emergency treatment of these cases and will not refer to the work of others Time is short and while no reference will be made to others' work, you may take it that many of my views are founded essentially on the experience of others as expressed in their writing

THE CHOICE OF CASE FOR SURGICAL INTERVENTION

It is rarely that surgery is required Those cases of over 40 years of age, which show a tendency to hæmorrhage, when the ulcer is seen by radiology to be a large one, and is a gastric ulcer at that, should be presented for operation as interval cases They should be selected and treated as " cold cases," with all the advantages that accrue to the surgery of choice

The choice of the acute emergency will depend essentially on the response of the individual case to medical treatment I have taken as indications for operation two severe hæmorrhages, endangering the life of the patient, after the commencement of medical treatment This forms a fairly definite indication in itself The size of the hæmorrhage must be estimated, and this is sometimes difficult When hæmatemesis occurs the quantity actually vomited may be measured Its consistence and appearance will also indicate the amount of blood lost With melæna the colour of the stools and the number will help, but as a general rule a large melæna likely to endanger the life of the patient means the passage of dark red blood per rectum in an incontinent manner

The estimation of the Hb is not of any great value in estimating loss of blood, but I have found the fall in the blood pressure a good measure

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Read at a meeting of the Medico-Chirurgical Society of Edinburgh on 2nd May 1951

A fall of systolic pressure below 100 indicates a severe loss of blood, with a rise in the pulse rate to over 120 This selection of case will be modified by other considerations, such as the age and the site of the ulcer as shown by previous X-ray examinations

The number of hæmorrhages from which the patient has previously suffered will also sway one, for patients hardly ever die of their first hæmorrhage The more often hæmorrhages have occurred in the past history of the case the more likely is the present one to be fatal

Pain is another feature that may help in deciding the necessity of operation Hæmorrhage from a small acute ulcer is not usually associated with pain The presence of pain will tend to indicate that the ulcer has penetrated beyond the stomach or duodenum and that a large vessel outside these organs may be the source of the hæmorrhage Pain in the back is of particular significance indicating erosion of the pancreas

The more difficult type of case to select for operation is the one where the hæmorrhage occurs over several days The slow steady loss of blood over several days with a continuance of a systolic blood pressure of below 100 ultimately produces a state of affairs where the patient becomes apathetic and of a waxy colour and where recovery will not take place, in spite of repeated blood transfusions A change takes place in the patient which makes recovery unlikely There seems to be no satisfactory explanation for this condition but it is suggested that it is due to changes in the liver This type of case is seen for the most part in older patients, and the point at which intervention should take place is not clear cut

A blood pressure persisting below 100 for more than two days is an indication for surgery, and another important one is the Hb reading of below 40 for two days I have usually taken it that where hæmorrhage continues over a period of four to five days in spite of effective medical treatment surgery should be undertaken

It is in this type of case that the close association of a physician and a surgeon is desirable My close association at the Deaconess Hospital with Professor Hill and latterly with Dr Batty has been a very happy one and has meant a more careful selection of these cases Sometimes the final decision to operate has been founded on a hunch of the physician I would stress the importance of this close association of physicians and surgeons in treatment, for in the Royal Infirmary I have felt on occasions that the decision to operate on one of these cases—late at night—seeing the case for the first time—and alone without the help of a colleague—is a burden I should not be asked to carry

PREPARATION OF THE PATIENT

Once the decision to operate has been taken, preparation of the patient is of importance The stomach must be washed out This rather transgresses one of the rules of the physician that the stomach should be left at rest, but it must be resorted to rigorously to prevent regurgitation at the time of the operation It is better carried out in the surgical ward immediately before operation, and a tube should be left in the stomach The medical ward sisters are unlikely to carry this out as fully or as carefully as their surgical colleagues as it is against their training, and one of my disasters was due to failure to follow this simple necessity

Blood transfusion must also be given before operation It has been my experience that in a patient who is actually bleeding, any marked revival in his condition is not likely to be achieved until the bleeding point has been controlled Blood is, therefore, only given in such quantity before operation as to raise his blood pressure to such a level that the operation may be started Once the bleeding point has been secured more blood is given as rapidly as possible, so that the patient usually leaves the operating theatre in a much fitter condition than he entered it I have usually found 5 pints of blood to be sufficient for the operation—1½ pints before operation and up to the time of securing the bleeding point and 3½ pints after this stage has been completed The actual quantity must of necessity vary in the individual case, but I have usually asked for 5 pints to be ready from the Blood Transfusion service before embarking on the operation It may be necessary to have the blood running into two limbs, perhaps under pressure, for the final restoration of the patient This method of resuscitation conforms to that carried out by our colleagues the gynæcologists in cases of severe hæmorrhage actually taking place at the time of operation, in cases of ruptured ectopic gestation The blood transfusion is started slowly before operation and the blood is not run in rapidly until after the bleeding point has been secured This method of resuscitation is suitable for the patient who has lost blood rapidly from two very large hæmorrhages Although he may look so ill, once the bleeding point has been controlled and the blood is run in rapidly it is surprising how quickly he responds

In the older patient, who has been losing blood continuously over several days, more time must be taken to restore him for operation, and it is unwise to proceed until his blood pressure has been raised to 120 This may mean the administration of several pints of blood, which should not be run in too rapidly for fear of raising the venous pressure excessively, but it is to be expected that his condition will improve The bleeding point is evidently smaller and it is likely that the blood can be run in faster than it leaks out

Any X-ray evidence of the size and site of the ulcer that may be available is helpful by indicating where the difficulties in the operation may be encountered The choice of incision may be decided by the site of the ulcer, as I tend to use right paramedian incisions for duodenal ulcers and left for gastric ulcers

ANÆSTHESIA

It is the advance of anæsthesia that has made the success of the operation for hæmorrhage possible I have always made use of a general anæsthetic in these cases, and the actual choice has been left in the hands of one of my capable anæsthetists Largely thanks to Dr Gillies's training, there is in Edinburgh a large choice of anæsthetists, who are capable of giving the perfect anæsthetic, with full relaxation and with safety They also seem capable of managing the blood transfusions most admirably while at the same time they reduce the coefficient of anxiety of the surgeon to zero They, along with their mentor, are deserving of the highest praise and our gratitude for what they have made possible The only warning I would give is that a very small quantity of anæsthetic is required for the purposes of induction A few ccs of pentothal only will be required for the passage of the intra-tracheal tube

THE OPERATION

On opening the abdomen a search is made for the ulcer Usually the ulcer is found easily and is of such a size that there is no difficulty in locating it Always look for more than one ulcer

The disturbing case is where no obvious ulcer is present The small intestine and the colon will be filled with blood and it is necessary to exclude other causes for the hæmorrhage apart from ulcer Cirrhosis of the liver or œsophageal varices should be excluded In those cases where no ulcer is found and no other cause of hæmorrhage is evident I have proceeded at once to the performance of partial gastrectomy This may seem a rather drastic procedure, but the operation, if the case be correctly chosen, is a life-saving measure Further, one must remove those parts where an ulcer is probably present It is a gamble, but the odds on the bleeding point being in one of the usual places are considerable and it is a gamble one must take The opening of the stomach and search for a small ulcer, which may only be a few mm in diameter, is time consuming, will lead to contamination of the abdomen and may fail to disclose the ulcer The chances are that it will not be actually bleeding at the time the search is made, a further reason for failing to find it The finding of a small acute ulcer is difficult at a post-portem examination

I was strengthened in this decision by the moral support given by the orthopædic surgeons who teach that where a tear of a cartilage of the knee has been diagnosed, the cartilage should be removed at operation, although it may appear undamaged The tear will become evident as the operation proceeds I had thought a good deal about this, for when I was house physician with the late Professor Ritchie a case of hæmatemesis was admitted and died At the post-mortem a small acute gastric ulcer was found Next day when I went to show to my chief the ulcer in the specimen, which had been kept in preservative overnight, we could not find the ulcer He asked me how a mere surgeon would be able to find such an ulcer at operation, and this had decided him against surgery in such cases

The operation carried out in each case has been that of partial gastrectomy with division of the duodenum beyond the ulcer, in the case of duodenal ulcer Local attempts at the control of the vessel have not been attempted The appearance of the chronic ulcer with its tough wall and the vessel held open by the fibrous tissue has made me feel that anything other than complete freeing of the stomach and duodenum is not a practical procedure

The freeing of a chronic duodenal ulcer is difficult and yet I have stressed the necessity of controlling the hæmorrhage as soon as possible In these cases I have divided the duodenum proximal to the ulcer and passed my finger into the lumen of the duodenum and so into the ulcer This controls the hæmorrhage and makes the dissection of the duodenum from the pancreas much easier

In the last case marked in the series there was a very large gastric ulcer occupying the greater part of the posterior wall of the stomach This would have meant a very high partial gastrectomy indeed The stomach was separated from the ulcer and the margins of the large defect in the stomach were sewn together A partial gastrectomy removing little more than the pylorus was performed for the duodenum had already been divided and closed This was felt to be adequate in view of the patient being 67 years of age

Post-Operative Treatment

These cases are peculiarly liable to suffer from infections in the post-operative period The severe loss of blood before operation appears to lower their resistance so that infections of the wound, subphrenic abscess and lung infections may occur Penicillin and sulphonamides should therefore be given in full doses

Result

I have operated on 18 cases in the series, with 3 deaths None of the cases died as a result of loss of blood at the time of the operation and all the deaths were avoidable

The first death was due to aspiration of stomach content This, of course, was entirely avoidable and the accident was primarily due to my failure to see that the stomach was properly washed out

The second death was due to hæmorrhage from the line of suture—a further accident that was avoidable

The third death was due to the patient's developing an ulcer at the lower end of the œsophagus several weeks after operation A jejunostomy was performed to feed the patient and subsequently a coil of small intestine became twisted round this and she died of intestinal obstruction

The table shows the list of cases dealt with They are set out in the age groups, and also according to the type of ulcer There is one case in the twenties, 5 in the thirties, 5 in the forties, 3 in the fifties and 4 in the sixties

TABLE

Operations on Cases for Hæmatemesis

No	Sex	Age	Type of Ulcer	Result
1	M	25	Gastric ulcer (acute)	Recovered
2	M	33	Duodenal ulcer	Recovered
3	F	36	Gastric ulcer (acute)	Recovered
4	M	38	Duodenal ulcer	Recovered
5	M	39	Duodenal ulcer	Recovered
6	M	39	Duodenal ulcer	Recovered
7	M	43	Duodenal ulcer	Recovered
8	M	44	Duodenal ulcer	Recovered
9	M	45	Gastric ulcer	Recovered
10	M	46	Duodenal ulcer	Recovered
11	M	48	Gastric ulcer	Recovered
12	F	55	Duodenal ulcer	Died
13	M	57	Duodenal ulcer	Recovered
14	F	58	Duodenal ulcer	Died
15	M	64	Duodenal ulcer	Recovered
16	M	65	Duodenal ulcer	Died
17	F	67	Duodenal ulcer	Recovered
18	M	67	Gastric ulcer	Recovered

Total —Gastric ulcer—5 , Duodenal ulcer—13

Five cases were due to gastric ulcer and in 2 the ulcer was a small acute one, only a few mm in diameter, where the operation proceeded in the absence of any demonstrable lesion on inspection of the outside of the stomach and duodenum One other case was an acute duodenal ulcer, not demonstrated until after the operation

INDIVIDUAL CASES

Criticism may be offered of operation in the case of the patient of 25 years of age, who was under the care of Dr Alexander

I give an abstract of the history of this case, showing the short history and the repeated hæmorrhages which pointed to a small acute ulcer It will be noticed that while operation was suggested after the fourth hæmorrhage, it was not undertaken till after the sixth hæmorrhage The cause was a small acute gastric ulcer, found in the specimen after operation

This patient was probably refused operation for a little too long, for he had reached the stage where his resistance to infection was considerably lowered and he developed, in spite of antibiotics, first a subphrenic abscess and later an empyema which required resection of a rib He made a full recovery ultimately

A W—Aet 25 years Three Weeks' History

13th July 1949	Hæmorrhage while at work
14th ,, ,,	Further hæmorrhage
15th ,, ,,	No hæmorrhage
16th ,, ,,	Severe hæmorrhage
	ADMITTED TO HOSPITAL
	Further hæmorrhage
	Operation suggested but not advised
17th ,, ,,	No further hæmorrhage
18th ,, ,,	Hæmorrhage at 2 00 a m
	Hæmorrhage at 6 00 a m , blood pressure 80 , pulse rate 130
	Operation performed at 10 30 a m

The only other case I would refer to in detail is No 8 in the table, as an example of the power of recovery of these cases

He gave a ten-year history of indigestion He was admitted on 6th March 1951 to the medical hospital suffering from hæmatemesis and melæna He was treated with morphia and blood transfusions, and at 2 a m on 7th March 1951 I was asked to consider operation The blood pressure reading was 90 and the pulse rate 120 By 9 a m his condition was fully restored with a blood pressure of 120 and pulse rate of 90 Operation was suggested, and I agreed to operate at 12 noon, but by this time he had had a fourth hæmorrhage and his condition was desperate I operated on him at 1 p m under the circumstances shown in Fig 1

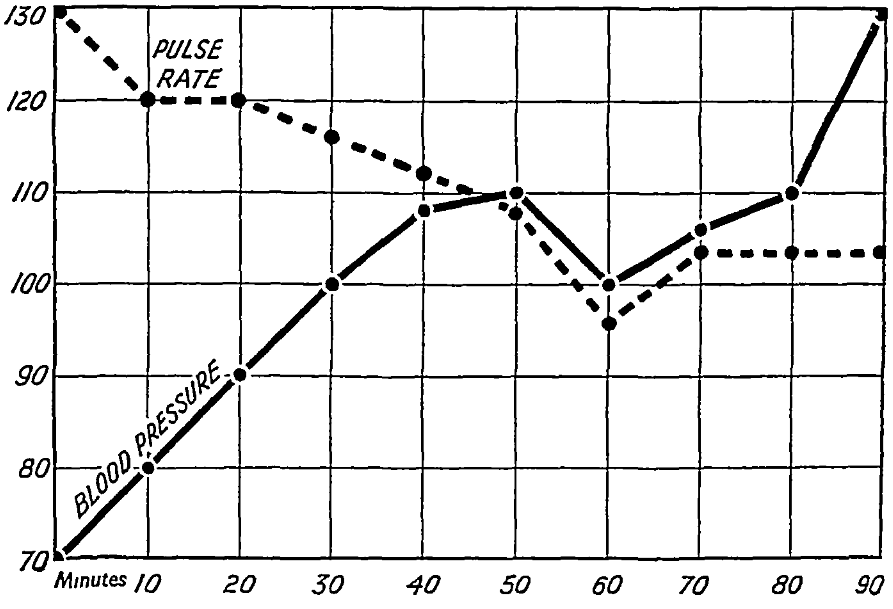

FIG 1—12 Pints of blood

The details of this case are presented to show how rapidly such a patient's condition may deteriorate and how essential it is not to delay operation once the decision has been made and when the patient's condition has been restored It also shows how far resuscitation may succeed in an ill patient

SUMMARY

(1) The surgeon's role is a very minor one in cases of hæmorrhage from a peptic ulcer He should endeavour to select, with the help of the physician, the 5 per cent of cases that are likely to die as a result of the hæmorrhage I feel that cases that show a tendency to bleed should be presented as " cold cases " before the life endangering hæmorrhage has taken place

(2) Two severe hæmorrhages after the institution of medical treatment or continuous bleeding for four or five days while under medical care in hospital have been taken as indications for operation, the old patient being considered for operation earlier, particularly where there is radiological evidence of a large ulcer

(3) In the absence of any demonstrable lesion in the stomach or duodenum, once other causes of hæmorrhage have been excluded, partial gastrectomy should be carried out It is a fairly certain expectation that the acute ulcer will lie in one of the usual situations and one must take a gamble that it will be Beware of multiple ulcers

(4) In the post-operative period infective complications are particularly likely to occur, and suitable precautions should be taken

These cases were dealt with in the Deaconess Hospital and in the Royal Infirmary of Edinburgh , the latter cases in the wards under the charge of Mr W Quarry Wood I would express my grateful thanks to Mr Wood for his constant help and advice in their treatment and for his permission to publish them

DISCUSSION

Mr Quarry Wood said that agreement seemed to have been reached as regards the principal indications for surgical treatment , these were—bleeding from a large vessel which does not respond in a short time to treatment by transfusion and, secondly, recurrence of the bleeding after a single massive hæmorrhage It was usually thought that bleeding was not dangerous under the age of forty, but several of Mr Adamson's cases had shown that it might be so He had been much impressed by one of Mr Adamson's cases, the man whose blood pressure had fallen to 70 before he was operated on He had seen this man in the theatre before operation and he was pale, cold and pulseless and appeared moribund He was given blood simultaneously into the arm and the leg, and Mr Wood felt that he owed his life as much to Dr Robertson, the anæsthetist, who succeeded in getting 12 pints of blood into the patient quickly, as to the operator He was sure that the best operation in cases of hæmorrhage was partial gastrectomy , the operation was often particularly difficult in these cases and should only be attempted by those who were thoroughly familiar with the procedure

Dr G J Alexander said that the subject inevitably recalled occasions when one was summoned to cases of severe hæmatemesesis or malæna in country practice many years ago There were no " flying squads " then and blood transfusion was limited to hospital practice The country doctor's main armamentarium was his hypodermic syringe with morphia, and this was supplemented, in severe hæmatemesis, by running in tap water to the bowel with a Higginson syringe and rubber catheter—we carried no saline or transfusion apparatus for intravenous administration of saline Yet some of these cases recovered—and were later fit to travel to hospital for further treatment The position is much better nowadays, but while we have heard a great deal about the treatment successfully given to these cases in hospital, it is after all the family doctor who is usually the first person to be called to them What should the general practitioner do in such emergencies to save life and to restore the patient to a state in which he can be taken to hospital ?

Mr A G R Lowdon said that he wished to refer particularly to the treatment of acute gastro-duodenal hæmorrhage due to peptic ulcer A review of 355 cases of bleeding peptic ulcer, which he and Mr I E W Gilmour had just completed, included 308 treated medically and 47 treated by emergency surgery the mortality rate in these two groups was 8 8 per cent and 31 8 per cent respectively, the over-all mortality being 11 8 per cent The high mortality in cases treated by operation was due to the fact that most of the cases selected for emergency surgery were desperately ill In the medically treated cases only 2 patients under 50 years of age died, but 31 of the patients treated by emergency surgery were under 50 years of age and of these 8 died Of 143 patients over 50 years of age who had been treated medically, 25 (17 5 per cent) died The mortality was higher in patients with gastric ulcer, patients with massive hæmatemesis and patients who were severely shocked on admission, and he thought that any of these features in a patient over 50 years of age should lead to immediate surgery being considered The mortality was also high in patients who had continued or recurrent bleeding in hospital, but to wait for this as an indication for urgent operation in older patients was often to wait until they were bad surgical risks

In patients under 50 years of age surgery would be less frequently indicated but should probably be advised for all cases of rapidly exsanguinating bleeding and for those younger patients who had continued or recurrent bleeding under treatment If this last (delayed) indication for emergency surgery was to be adopted in patients under 50 years of age, the medical treatment should include adequate blood transfusion so that the patient would not become a poor surgical risk before the need for operation was manifest

Dr Card said there seemed to have been three definite advances in the treatment of hæmatemesis Firstly, a return to feeding as opposed to starvation , secondly, the use of adequate—and he would stress the word " adequate " —blood transfusion , and thirdly, gastrectomy as an emergency operation for the proper type of case He felt it was of great value if surgeon and physician could see these cases together, and there was no doubt that surgery could save a number of patients Such cases occurred in the oldest age groups, particularly if there was severe bleeding from a single vessel , this might be suspected clinically by the sudden collapse of a patient who had previously rallied to transfusion He pointed out the difficulty that could occur at operation, when the surgeon, even by palpation, could not be certain of the existence of an ulcer , a gastrectomy then had to be " blind "

Dr Batty in reply stated that although the principles of treatment of bleeding peptic ulcer were now generally accepted, much depended in their execution upon the personality of the medical attendant There was often a tendency to extreme conservatism that was not always in the best interests of the patient Each patient should be treated individually without hard and fast rules based upon his age and the number of hæmorrhages he had sustained Concerning treatment to be adopted by the general practitioner, little was required other than sedation and controlled dietary in some two-thirds of the cases Although intake by mouth was regulated largely by the wishes of the patient, it was desirable to establish as soon as possible a fluid balance A feeling of marked nausea often indicated continued bleeding In the severe case, transfusion was a necessity, and in this country facilities were generally available for the rapid removal of the patient to hospital In their absence untreated continuing severe hæmorrhage must entail loss of life as demonstrated in the autopsy series That gastroscopy had not been mentioned in the discussion was very satisfying as this procedure was not indicated in acute hæmatemesis

SURGICAL ASPECTS OF VOMITING IN THE NEWBORN

By J J MASON BROWN, O B E , F R C S E
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When you did me the honour of inviting me to address the Medico-Chirurgical Society on a subject of my own choosing you gave me the invaluable opportunity to pause to take stock of the work of my charge in the Royal Hospital for Sick Children during the past five years In doing this I was on the look-out for a subject which would be of interest not only to the surgical members of the Society but also to those whose work lies in other branches of medicine Very few members of our profession are able to make original contributions to the advancement of medicine and, although I am conscious that I have nothing new to contribute to-night, I hope that a review of our experience in one small segment of the wide field of pædiatrics may be of assistance to some of my audience Should my remarks lead to the earlier recognition of even a few neonatal obstructions I shall be more than satisfied and it is this hope which has given me the courage to address you on this subject to-night

Many, and indeed most, of the newly born babies who vomit do so from causes which do not require surgical treatment, *e g* after difficult labours, forceps deliveries, etc In those in whom a surgical lesion is present early operation offers the only possibility of cure As the infant's gut cannot tolerate distension or impairment of its blood supply for very long, perforation and peritonitis are early complications and do, in fact, sometimes occur before birth Delay is also dangerous in the incomplete obstructions because of the profound biochemical changes induced by persistent vomiting We strongly endorse Ladd's opinion that any newly born baby who vomits persistently and, particularly, any baby who vomits bile should be investigated fully without delay It is illogical to begin treatment without a diagnosis and, while the investigation to be described may not establish the exact cause of the vomiting, it will give sufficient evidence, in most cases at least, to exclude a lesion requiring operative treatment and medical measures may then be employed with confidence Before considering the investigation of these patients I propose to summarise the clinical material on which our conclusions are based The cases have been classified according to the type of lesion which was found at operation In some more than one anomaly was encountered, and these cases have been recorded only under the lesion which was considered to be most important

Read at a meeting of the Medico Chirurgical Society of Edinburgh on 6th June 1951

Œsophageal and ano-rectal atresias have been excluded and the cases restricted to those occurring within the first four weeks of life, somewhat arbitrary restrictions but necessary ones, to limit the number for presentation to-night

Neonatal Obstructions (Excluding Œsophageal and Ano-rectal Atresia)
1946-50

Faults in development of wall of alimentary tract —	
Complete obstruction—Atresia	4
Incomplete obstruction—Stenosis	1
Duplication	1
Extrinsic obstructions —	
Congenital bands and Meckel's diverticulum	3
Volvulus neonatorum	8
Hernia—Internal—diaphragmatic	4
External—strangulated inguinal	6
Faults in bowel content —	
Meconium ileus	4
Neuro-muscular ? —	
Pyloric stenosis	35
Enterospasm	2
Hirschsprung's disease	3
	71

From the surgical point of view a complete investigation must seek to establish the presence or absence of any of these anomalies

THE INVESTIGATION OF THE PATIENT

The diagnosis must be based on an accurate history, clinical examination, radiological investigation and the examination of the vomitus and stool The history should include the family history and that of the labour as well as the post-natal symptoms

The time of onset of the vomiting gives some indication not only of the site of the lesion but also of its nature, *e g* lesions high in the alimentary tract and complete obstructions cause earlier vomiting than more distal or incomplete ones

The presence or absence of bile in the vomitus indicates whether the lesion is below or above the ampulla of Vater The absence of bile, the frequent choking on its own mucus, the relief of cyanosis by repeated aspiration, and the almost constant presence of a finely aerated froth on the baby's lips point to œsophageal atresia If the baby fares normally at first and the vomiting begins mildly in the second or third week, becoming progressively more severe and, ultimately, projectile and does not contain bile, the answer is almost certainly pyloric stenosis

Duodenal obstruction, due either to extrinsic or intrinsic factors, occurs most frequently below the ampulla of Vater so that the vomit is usually bilious The vomiting begins early in complete intrinsic lesions, but in incomplete lesions and in volvulus neonatorum it often does not begin until the third day or even later

Stool —Meconium of normal colour is passed in incomplete obstructions, but the stools become less frequent and smaller and may cease entirely In meconium ileus meconium is not passed, and in Hirschsprung's disease its passage is delayed, while in ano-rectal atresia meconium is either not passed at all or it escapes from an abnormal site In complete obstructions small dry greyish-green stools or a mucous cast of the contracted bowel distal to the obstruction may be passed spontaneously or, more often, following rectal examination In addition, microscopic examination of stained smears taken from the central part of such a stool fails to demonstrate any lanugo hairs or stratified squamous cells derived from the liquor amnii which are constant features of normal meconium

A family history of the death of siblings in infancy from intestinal obstruction or staphylococcal respiratory infection points strongly to congenital fibro-cystic disease of the pancreas, of which meconium ileus is an early and severe manifestation

Clinical Examination —Upper abdominal distension may be found in œsophageal atresia with œsophago-tracheal fistula, pyloric stenosis or obstruction in the duodenum or upper jejunum Gastric or duodenal peristalsis may be seen in the more chronic high obstructions Diffuse abdominal distension may be the result of perforation with pneumoperitoneum or meconium peritonitis, or of low small intestine and upper colon obstructions A grossly distended transverse colon, which may show well-marked peristalsis, has been observed in low partial obstructions of the rectum, or recto-sigmoid (Hirschsprung's disease) Pre-natal perforation and meconium peritonitis may cause distension of such severity that there is difficulty in delivering the baby, It might be worth while to interpolate a warning at this point, namely that the absence of distension does not exclude an obstructive lesion, as some babies seem to be able to keep the upper loops virtually empty by the ease with which they vomit

In large diaphragmatic herniæ the abdomen is usually much smaller than one would expect for the size of the infant

Palpation of the abdomen may reveal the doughy coils of ileum distended by meconium in meconium ileus, the presence of a pyloric tumour which may be felt to harden under the fingers, or, rarely, a cystic duplication may be felt The hernial orifices must be examined with care, particularly the inguinal ones, in premature babies, for in them strangulated or incarcerated inguinal hernia is not uncommon Tenderness is, of course, difficult to assess, but there is rarely any tenderness or muscle in guarding in uncomplicated cases

The clinical examination is concluded by the examination of the rectum and the chest In most newborn babies of average size the little finger can be used for rectal examination It must be employed with gentleness and serves to exclude ano-rectal atresia and will recognise the contracted empty rectum of neonatal Hirschsprung's disease (a feature also found distal to complete obstructions) Examination of the chest will record moist sounds in the right lower lobe in late cases of œsophageal atresia and the displacement of the heart, dullness or hyper-resonance and, possibly, the presence of intestinal sounds in diaphragmatic hernia

Enough has been said to show that the diagnosis is possible by clinical methods alone in most cases of pyloric stenosis and in some cases of obstruction at other levels, but in many we require additional information and this is available to us by means of X-ray examination Immediately after birth the normal baby begins to swallow air and within a few hours the X-ray film shows air fairly evenly distributed throughout the alimentary tract (Fig 1) In the investigation of suspected obstruction, anteroposterior and lateral views are taken in the erect and head-down positions As gas or air will rise to the highest point, if given time to do so through viscid meconium, the second view may reveal the exact site of the obstruction (Figs 2, 3) The straight film will also demonstrate the presence of pneumoperitoneum and may also show the calcification characteristic of pre-natal meconium peritonitis If the straight X-ray shows gas shadows fairly evenly distributed, but the history and clinical findings suggest the possibility of an obstruction below the level of the pylorus, an opaque medium may then be given and followed by X-ray Barium should be avoided in the newly born baby because its aspiration is followed by a fatal pneumonia (Fig 4) Furthermore, if a watery solution of barium of the usual consistence is given it cannot be removed, and inspissated barium may occlude the lumen of the contracted segment of gut below a complete lesion following a successful short circuit procedure We have employed lipiodol, which is given by means of a stomach tube and have been fairly well satisfied with its use

This completes the investigation of the patient, and it should be possible in most cases, after correlating the clinical features and the X-ray findings, to decide whether there is an obstruction requiring surgical correction and also to have a shrewd idea of its site and nature

Too much has been made of the risks of operating on such small babies and all too often they are referred too late, surgery being regarded as a last forlorn hope It cannot be emphasised too strongly that newly born babies tolerate major surgical procedures very well and the danger is not in laparotomy but in leaving it too late I believe that if, following a full investigation, there still remains a reasonable doubt about the diagnosis of incomplete obstruction it is safer to explore the abdomen than to delay until the baby's condition has deteriorated and the diagnosis is all too obvious While it is true that small babies tolerate operations well they do so provided only that certain precautions are taken

Pre-operative Treatment —A tube must be passed and the stomach

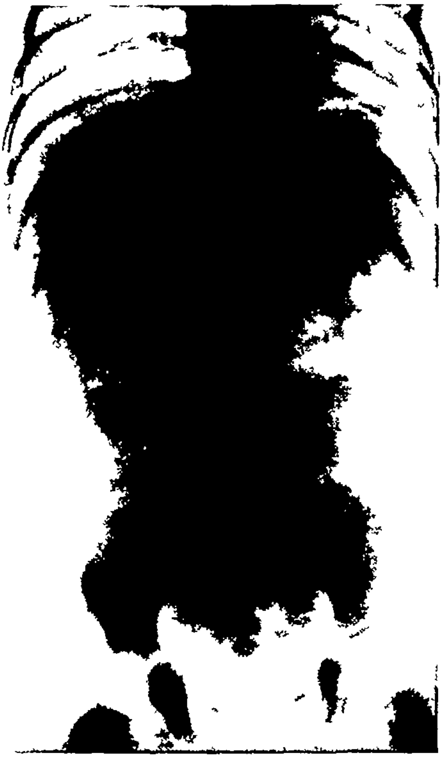

FIG 1 —Radiograph of normal baby twelve hours after birth

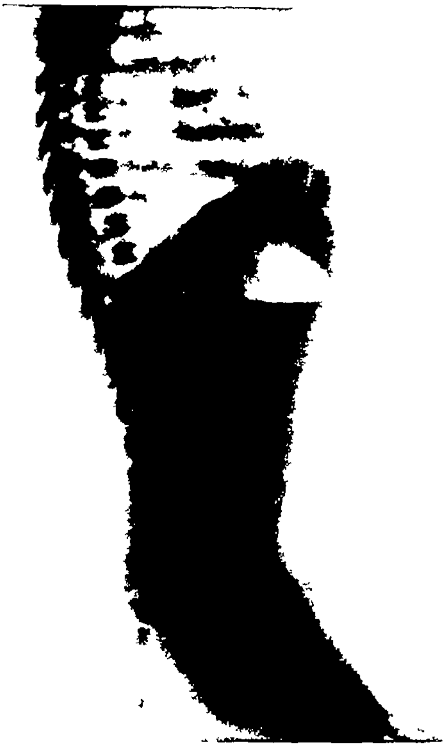

FIG 2 —Air outlining stomach Apart from two small gas shadows remainder of gut contains no air Incomplete duodenal obstruction due to volvulus neonatorum

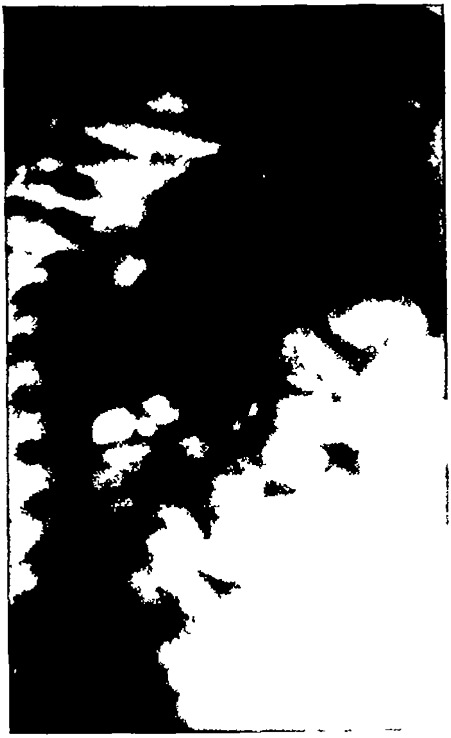

FIG 3 —Gross distension of small bowel in atresia of lower ileum

FIG 4 —Illustrates the danger of giving barium to the newly born baby Note barium in bronchi

emptied before the baby is taken to the theatre The tube should remain *in situ* so that aspiration may be repeated as required, and, when necessary, the tube is available to the surgeon to demonstrate the patency of the duodenum

The blood volume of newborn infants is small, and meticulous hæmostasis does not prevent the loss of an amount of blood which, although small, is a greater proportion of the blood volume than in the adult It is our practice to set up an intravenous drip beforehand so that blood can be given as soon as it is indicated

The prothrombin level in normal infants falls progressively up to the fifth day and rises to normal again about the eighth day, and, as persistent vomiting delays the rise in prothrombin, vitamin " K " should be given before operation

Again, the relatively huge surface area and the instability of the temperature regulation of small and, more particularly, premature babies makes them tend to adopt the temperature of their environment so the theatre must be warm and the operating table may be heated Anoxia must be avoided and oxygen may be given before and after operation and may help to lessen the distension

The Anæsthetic —Initially, it was our practice to operate under local analgesia but we have abandoned this method If the baby is not sedated it may cry, when the prolapse of coils of intestine makes suture of the abdominal wall difficult or impossible and may even require the induction of general anæsthesia Sedation which is certain to be adequate for the operation will result in delay in the return to full activity of the vomiting reflex, and aspiration of vomitus may occur without being recognised during this stage, even in the presence of trained observers, and this was, in fact, a common cause of death We believe, therefore, that the ideal is for the baby to be fully awake both on reaching and on leaving the operating table, and that the only time its reflexes can be allowed to be depressed is while it is in the hands of a skilful anæsthetist The anæsthetic agent must permit of adequate oxygenation and it must be eliminated rapidly We have used cyclopropane and have found it satisfactory The operation for pyloric stenosis lasts only a few minutes, so we employ local analgesia in addition in order that the anæsthetic may be stopped as soon as the peritoneum has been closed and the baby is wide awake as the skin is sutured The baby must be fully awake and crying lustily before it leaves the hands of the anæsthetist, who has at his disposal endoscopes of suitable size and, what is more important, is fully competent to use them Endotracheal anæsthesia is employed when indicated

Infection —All small babies are vulnerable to infection, and prophylactic antibiotic therapy is given in an attempt to prevent it These babies should be nursed in cubicles and if these are not available they should be nursed under a strict bed isolation regime

The Operation —The diagnosis of pyloric stenosis is seldom in doubt and a small incision is adequate for pyloromyotomy In other cases, despite the preliminary investigation the operation is to a certain extent exploratory in nature and the exposure must be really adequate and can be obtained by a paramedian or a transverse incision When the vomitus has never contained bile the lesion will be above the ampulla of Vater, so that the pylorus and duodenum are examined first Bilious vomiting may be due to a wide variety of causes and it is vitally important to have a knowledge of the possibilities in order to carry out a planned examination of the alimentary tract

If, on opening the abdomen, there is an escape of gas or intestinal content the site of the perforation is sought immediately to try to prevent further leakage The common sites for perforation are the ileum and cæcum and also the second part of the duodenum, but in the latter the indwelling gastric tube is usually adequate to prevent the further escape of content (Glover and Barry, 1949) If perforation has not occurred the operation proceeds systematically to establish the type and site of the obstruction

When there is no sign of the transverse colon and the entire abdomen appears to be occupied by coils of congested small bowel the condition is that of volvulus of the mid gut loop (volvulus neonatorum) Such a volvulus cannot be undone within the abdomen and the whole of the small intestine is delivered on to the abdominal wall, where it is rotated anti-clockwise until the transverse colon comes to occupy its normal site, and the cæcum comes to lie in the right hypochondrium where it is attached by the hepato-colic ligament The cæcum in this position overlies and obstructs the third part of the duodenum, a type of extrinsic duodenal obstruction which may be present without volvulus, and which requires the full exposure of the duodenum to be described

If the transverse colon and cæcum are in their normal sites the next step is to seek the level to which distension extends If only the stomach and duodenum are affected the lesion will be found proximal to the ligament of Treitz Having excluded undiagnosed pyloric stenosis and confirmed the absence of small intestine volvulus by examining the root of the mesentery and confirming the normal position of the cæcum, the next step is to explore the duodenum This is done by separating the secondary attachments of the hepatic flexure and the ascending colon and displacing them to the left (Ladd, 1933) The attachments of the duodenum to the abdominal wall and base of the mesentery at the superior mesenteric vessels and at the ligament of Treitz are divided, thus freeing the duodenum so that it runs downwards on the right side of the abdomen and widens the base of the mesentery and thus helps to prevent recurrence of the volvulus (Glover and Barry, 1949) Only in this way can one be certain that no extrinsic obstruction is missed If gas does not now pass freely into the small gut there must be an intrinsic obstruction, and this may be proved by the failure to pass the tube from the stomach into the small gut If the stomach and duodenum are greatly dilated gastro-jejunostomy is indicated for obstructions above the ampulla of Vater which are rare, but duodeno-jejunostomy is the better procedure for obstructions below it In rare instances a membranous diaphragm may be excised by a plastic procedure (Morton, 1939)

If the small intestine is distended the obstruction is most frequently in the ileum or in the proximal colon Obstruction in the ileum may be due to atresia, stenosis or meconium ileus If the obstruction is in the lower ileum and the distended coil is full of thick doughy material, while the ileum distally has a beaded appearance due to inspissated lumps of meconium and the colon has the characteristics of microcolon, the condition is meconium ileus The first step is to make sure that there is no volvulus of the distended loop, and the gut is then cleared of its contents through one or more enterotomies These are closed and the gut is returned to the abdomen

When an atresia or stenosis is found the gut distal to it should be examined to exclude multiple lesions The contracted distal gut is then distended by the injection of air or fluid in order to make it as large as possible to facilitate anastomosis to the upper distended loop which should be resected when there is the least doubt about its viability Wherever possible end-to-end anastomosis should be done to avoid leaving blind loops which may give rise to trouble in the future as shown by one of our patients

Six years after resection of an irreducible ileo-colic intussusception with closure of the bowel ends and lateral anastomosis the girl was admitted to the medical side of the hospital because of severe secondary anæmia The only positive findings, apart from this, were a persistently positive Benzidene test in her stool and an incisional hernia The hernia was repaired and the bowel was examined The blind loops had obviously continued to grow with the child They were resected and an end-to-end anastomosis was made Investigation of the blind loops showed numerous ulcers of the mucosa The child's blood rapidly became normal and has remained so and she says she " has not got a tummy any more," thus suggesting that she had never known what it was like to have freedom from abdominal symptoms and accepting this as normal had never complained

In the case of occlusion by diaphragm the best procedure is to open the gut and remove it

All anastomoses should be made with fine atraumatic interrupted silk sutures

When the distension involves the large intestine the lesion will be ano-rectal atresia (which should have been diagnosed pre-operatively), atresia of the colon or Hirschsprung's disease In this latter condition it may be possible to demonstrate the funnel-shaped junction between the distended bowel and the lower contracted segment when the treatment is either transverse colostomy or, as advocated by Swenson and Bill (1948), immediate recto-sigmoidectomy It must be emphasised that the acute obstructive phases of this condition are recognisable clinically and they can be relieved by the passage of a catheter per rectum Operation is deferred until decompression has been secured

Time does not permit a full discussion of the post-operative care It is usually stated that wound disruption is a common occurrence, but, following the use of silk for the closure of the fascial layer, this has not occurred The indwelling stomach tube is of great value in preventing distension by swallowed air and the fluid balance may be maintained by intravenous infusion or by subcutaneous injection with the use of hyalase

RESULTS OF TREATMENT

Diaphragmatic Hernia—The hernia which causes symptoms at this period of life is the large postero-lateral one through the foramen of Bochdalek There may be vomiting, distress following feeding relieved by placing the baby on the side corresponding to the lesion, or merely failure to thrive In a large hernia, dyspnoea or cyanosis may be noted A straight X-ray is sufficient for diagnosis and the presence of a hernial sac may be inferred when lung tissue is visible above the lesion, whereas in the absence of a sac abdominal viscera reach the apex of the chest Hedblom has stated that 70 per cent of these babies die within the first year of life, so that operation is indicated once the diagnosis is made Early operation means the absence of adhesions within the chest, and an abdominal approach allows the surgeon deliberately to leave a temporary incisional hernia if the tension within the abdomen would be too great were it required to accept a large amount of gut which it had not accommodated previously Another reason is one that I have not seen mentioned previously and that is that in one of our cases there was, in addition, an extrinsic duodenal obstruction which was treated at the same time Four such cases were encountered, three on the left side and one on the right All the left-sided cases were cured by operation The large right-sided hernia contained the right lobe of the liver, the small intestine and part of the large bowel The baby gained weight slowly for three weeks following operation but, thereafter, did not thrive and died forty-six days after operation, autopsy revealing a satisfactory hernial repair and no definite cause of death

Pyloric Stenosis—The majority of these babies are seen over the age of four weeks and all too often they are seen after the feeds have been chopped and changed Of the 35 under the age of four weeks, 33 recovered Of the 2 who died, one (aged two weeks) had been investigated with barium before admission and died four days after operation from severe pneumonia, the other (aged three weeks) died three weeks later from gastroenteritis, autopsy showing satisfactory relief of the obstruction That these babies stand operation well is shown by the smallest baby in the series, who weighed 2 lb 12oz at operation, and whose post-operative course was uneventful

Intestinal Obstructions (excluding diaphragmatic hernia—32 with 15 deaths) —Six were babies with strangulated inguinal herniæ, all of whom recovered, probably because the visible swelling led to all being referred early for treatment

Of the 4 infants with complete atresia of the intestine, one (ascending colon) survived, one (third part of the duodenum) treated by duodeno-jejunostomy at the age of six days, died nearly four weeks later, no definite cause being found to explain the death, one (ileum) had hæmatemesis and rectal bleeding at six hours associated with multiple petechiæ and was apparently relived by transfusion The vomiting ceased, and I was asked to see her, aged six days, with marked distension and with small intestine peristalsis, a complete atresia of the ileum was short circuited, the baby dying nineteen hours later, the anastomosis being intact and the only positive autopsy findings being bilateral pulmonary œdema and jaundice The fourth patient had multiple atresia of the ileum, a mild pre-natal meconium peritonitis and a loop of ileum of doubtful viability Death was due to peritonitis following leakage at one of the anastomoses where the gut had proved not to be viable

Of the 3 patients with obstructions due to congenital bands or Meckel's diverticulum, one died from infection of the alimentary tract (the only finding at post-mortem examination) forty-four days after operation, having survived a second operation for wound disruption

All 4 babies with meconium ileus died, one being inoperable because of a severe pre-natal meconium peritonitis, while 2 died from respiratory infections after their obstructions had been successfully relieved It is interesting to find the " microcolon " completely normal in appearance at autopsy in such cases

Of the 3 patients with neonatal Hirschsprung's disease, 2 died, one, a premature baby weighing 3 lb 4 oz, following transverse colostomy and the other in whom no organic obstruction could be found at laparatomy died subsequently from perforation of the cæcum If the 2 autopsy specimens and in the one biopsy specimen of the distal segment Dr Macgregor has confirmed the absence of ganglion cells and the presence of abnormal nerve trunks in the region of the myenteric plexus In one of the autopsy specimens there was no macroscopic evidence of the narrow lower segment described by Stephens *et al* (1949)

Volvulus neonatorum deserves special mention Three of our 8 patients died One, a premature twin had vomited for four days before admission during which he had received eumydrin He died thirty-six hours after operation from bilateral broncho-pneumonia which was present on admission, while autopsy confirmed that the gut was viable and the obstruction had been relieved, the second had vomited bile from the third day of life and was admitted aged three weeks, the volvulus was reduced but the gut was of doubtful viability and was found to be non-viable at autopsy The third patient had vomited bile for four days, operation was uneventful and he died suddenly the following day, probably from aspiration, but autopsy was not granted Two of the 3 deaths were, therefore, attributable to delay in diagnosis It is gratifying to me that we have had some success in this type of duodenal obstruction, because it was my former chief, Professor Dott, who was the first to explain the etiology of the condition and the first to diagnose it clinically and to treat it by operation

Prognosis —This record cannot be regarded complacently because 18 of the 71 babies who presented with vomiting due to " surgical " lesions died, *i e* 25 3 per cent If those suffering from pyloric stenosis are excluded because of the much better prognosis in this condition, the mortality rate is 44 per cent As this figure then places undue emphasis on the hopeless cases I believe it is preferable to regard it not as a 44 per cent mortality rate but as a 56 per cent survival rate, for the ultimate prognosis in successful cases (other than in meconium ileus) is nothing less than a normal expectancy of life—surely a great incentive to all who are responsible for the care of the newborn to distinguish between the " medical " and " surgical " types of neonatal vomiting, and to secure the earlier treatment of babies with organic obstructions

SUMMARY AND CONCLUSIONS

(1) Early diagnosis and operation afford the only chance of relieving neonatal obstruction

(2) In order that the diagnosis may be made in time all babies who vomit persistently and all who vomit bile must be investigated fully without delay

(3) If, following negative investigations, there is still a reasonable doubt, laparotomy is less dangerous than procrastination

(4) Newborn babies tolerate major operations extremely well

(5) The operation must be planned in such a way that the cause of the obstruction will be found without delay and multiple lesions will not be missed

(6) Gentleness and speed are important in these procedures, but of the two speed is less important

(7) The prognosis following successful operation is a normal expectancy of life

In conclusion, I should like to acknowledge the debt I owe to my colleagues Miss R Mackay and Mr F Robarts for allowing me to refer to patients who were treated by them, to Drs Shannon, Dummer and Bell for their skilful anæsthesia, to my medical and obstetrical colleagues for their co-operation, and above all to Dr Agnes Macgregor who has done so much to help us to learn from the unsuccessful cases

REFERENCES

GLOVER, D M , and BARRY, F McA (1949), *Ann Surg* , 130, 480
LADD, W E (1933), *Journ Amer Med Assoc* , 101, 1453
MORTON, J J (1939), *Surg Gynec Obstet* , 68, 257
STEPHENS, F D , BODIAN, M , and WARD, B C H (1949), *Lancet*, 1, 6
SWENSON, O , and BILL, A H Jr (1948), *Surgery*, 24, 212

DISCUSSION

Professor Sir James Learmonth congratulated Mr Mason Brown on a most interesting and lucid paper, and said he was pleased that Mr Mason Brown had laid the emphasis on the survival rate of these patients after operation rather than upon the mortality rate, because without operation the outlook was hopeless whereas with operation many of them could look forward to leading normal lives The work of surgeons in the Royal Hospital for Sick Children had always been outstanding in British surgery, and he was sure that Mr Mason Brown was continuing the great tradition

Dr Douglas Nicholson pointed out that there were only a few symptoms that a baby could show, *e g* either vomiting, constipation or diarrhœa The explanation of these symptoms should be fairly easy although they were often wrongly interpreted The baby's facial expression should tell the examiner a good deal, and the soft thin abdomen was easy to palpate He thought that the congenital malformations and obstructions in the alimentary tract were often missed owing to lack of awareness by the doctors of these conditions in the small infant

He was closely associated with Mr Mason Brown in his work and had seen many of these cases with him He congratulated Mr Mason Brown on his admirable presentation of the subject, and hoped the attention that had been drawn to the diagnosis and treatment would prove a valuable contribution for those who were dealing with the young infant A careful history and examination with that awareness of the possible conditions for such symptoms should lead to the correct and early diagnosis Some of the conditions described were more common than might be supposed, *e g* on the average there were about 30-35 cases of congenital pyloric stenosis per ward per year seen at the Royal Hospital for Sick Children

Dr J L Henderson said that he had recently seen three premature babies with pyloric stenosis who weighed 3-4 lb at birth, the smallest being 2 lb 12 oz at the time of operation The clinical features are slighly different at this age , instead of the usual good appetite, the appetite falls off, there is no characteristic forceful vomiting and peristalsis may not be abnormally pronounced The important features, then, which should make one suspicious of pyloric stenosis in premature infants are the age of onset of the vomiting, the steady loss of weight and the constipation Once the condition is suspected the abdomen should be examined for a tumour

Dr John Thomson emphasised that meconium could be passed through an opening of no greater size that would admit an ordinary silver probe This opening might well be abnormally situated and thus mask for a time the presence of an imperforate anus

Dr Batty agreed that vomiting in infancy was commonly due to causes of little interest to the surgeon Such material could obviously not be included in the present paper The outstanding case at the Deaconess Hospital coming within the scope of the discussion was referred as an example of the " blue baby " of congenital heart disease Without vomiting or other complaint, the infant was shown by radiography to have a large right-sided diaphragmatic hernia

Mr Mason Brown, replying, said that all his cases of strangulated hernia were in premature babies and the increased incidence is due in all probability to the increasing number of premature babies now saved

So long as lipiodol is given by stomach tube, it is safe If an obstruction is present, the lipiodol can be removed, if there is not, it is quickly passed The only disadvantage is the fact that it tends to float on the top of fluid

THE DIAGNOSIS OF ADDISON'S DISEASE

By T W G KINNEAR, M B E , M B , Ch B , M R C P (Ed & Lond)

ADDISON'S disease is a state of chronic adrenal cortical insufficiency which results from tuberculous destruction or idiopathic atrophy of the cortex of both adrenal glands Occasionally, replacement of the hormone-secreting cells by malignant tissue produces the clinical picture of Addison's disease, the glands being invaded directly by an intra-abdominal neoplasm or by way of the bloodstream in, for example, carcinoma of the lung We have seen one patient with Addison's disease who had positive serological tests for syphilis The association in this case was probably fortuitous, but a few cases have been reported in which syphilis was found, post mortem, to be the causative agent Addison's disease is not synonymous with cortical insufficiency, which may follow failure of the anterior pituitary gland to secrete its adrenocorticotrophic hormone

This paper is based on a study of 30 cases of Addison's disease who were admitted to Professor Dunlop's charge of the Royal Infirmary between 1939 and 1951 We have been personally concerned with the investigation and treatment of 21 of these patients We should like to thank Professor Dunlop, to whom we owe what knowledge we have of Addison's disease, for allowing us to talk about these patients here to-night

There were 16 female and 14 male patients The youngest patient was aged 14 and the oldest 53 , 80 per cent were between 20 and 50 years of age when they first appeared for treatment The majority *had had symptoms for between 6 months and a year before coming to* hospital Exceptionally, the history was as short as one month or as long as two years

The commonest present symptom (19 patients) was a feeling of weakness and tiredness Darkening of the skin was the first abnormality to attract the attention of 5 patients, all of whom were women On the other hand, a number of men of the labouring class had failed to notice pigmentation which was strikingly obvious to an outside observer Five patients consulted their doctors because of persistent vomiting, and one because of extreme mental depression

Whatever the presenting symptom, a feeling of tiredness and weakness was a feature of the history in every case (Fig 1) The only other constant symptom was loss of weight, sometimes amounting to only a few pounds but often to as much as one or two stone Gastro-intestinal symptoms were present in 80 per cent Apart from the

Read at a meeting of the Medico Chirurgical Society of Edinburgh on 6th February 1952

5 patients whose presenting symptom was repeated vomiting, 19 complained of anorexia and nausea, with or without occasional vomiting Abdominal pain was a symptom of ominous significance, as it usually heralded Addisonian crisis Most of our patients were hypoglycæmic in the early morning They were difficult to rouse from sleep and their attitude toward those who made the attempt was pathologically surly and resentful Nine patients reacted violently to the insulin which they secreted in response to a carbohydrate meal, so that an hour and a half to two hours after taking food they tended to become sleepy, to feel weak and faint, or to behave in the uninhibited manner of the mildly intoxicated

ADDISON'S DISEASE

Incidence of Common Symptoms and Signs in 30 Cases

	No of Cases	Per Cent
Tiredness and weakness	30	100
Loss of weight	30	100
Skin pigmentation	29	97
Blood pressure below 110/75	27	90
Gastro-intestinal symptoms	24	80
Early-morning hypoglycæmia	24	80
Buccal pigmentation	22	73
Attacks of reactive hypoglycæmia	9	30

FIG 1

Some abnormality of pigmentation of the skin was found in all except one case In a typical case brown pigmentation, which is due to an increased deposition of melanin in the deeper layers of the dermis, is most conspicuous on exposed parts like the face and neck and hands , on the nipples and in the perineum , and on areas subjected to pressure, such as the elbows, spine and scapulæ

The fundamental cause of the pigmentation in Addison's disease is not known with certainty It has been suggested that dioxyphenylalanine (DOPA), a derivative of tyrosine, is the common precursor of melanin and adrenaline , that destruction of the adrenal medulla occurs, and prevents the synthesis of adrenaline , and that consequently all the available DOPA is converted to melanin, which thus appears in excessive amounts in the skin This theory is almost too plausible to be true, but it fits the facts better than any other that has been proposed

On the dorsum of the hand the pigment is most marked over the knuckles Pigmentation of the palm is more selective, and is usually limited to the skin creases, especially those over the interphalangeal joints The depth of colour varies from a dark brown, almost negroid hue to a faint yellowish-brown tinge like fading sun tan The diagnosis of Addison's disease must be much more difficult in many parts of the world than it is in Scotland where we so rarely have to consider a physiological cause of skin pigmentation The pigmentation in Addison's disease is characteristically patchy rather than uniform in many cases, areas of increased melanin deposition alternate with patches of skin which lack even the normal amount of pigment, and which appear vividly white by contrast Occasionally it is this leucodermia, rather than any darkening of the skin, which first attracts the attention of the patient and of the physician Pigmentation of the buccal mucous membrane, if not pathognomonic of Addison's disease, is nearly so The pigment is usually seen best on the inner surface of the lip and cheek, on the gums and the hard palate, but in one case it was confined to the tongue It has been our experience that buccal pigmentation occurs only in cases in which the skin is obviously and typically pigmented, not in the less typical cases where its presence would be so much more helpful

No other single physical sign is as valuable as pigmentation in making the diagnosis, but the blood pressure may be a considerable aid The highest blood pressure we have recorded in an untreated patient is 120/90 mm of mercury Two-thirds of our patients had a systolic pressure between 90 and 110 mm and a diastolic pressure between 60 and 75 mm Extreme hypotension, therefore, is not an essential feature of the disease, but a pressure above the normal range is a strong point against the diagnosis

Twenty-one of our patients (70 per cent) conformed to the classical pattern which I have outlined They presented little diagnostic difficulty, and the clinical diagnosis was amply confirmed by their dramatic response to treatment with deoxycortone acetate (DCA) The only non-clinical investigation which was carried out as a routine in these patients was radiological examination of the abdomen The demonstration of calcification of the adrenal glands gives unequivocal proof of the diagnosis of Addison's disease and also of the tuberculous ætiology of the condition, though, of course, a negative X-ray does not exclude adrenal tuberculosis

A variety of tests of adrenal cortical function is available for the diagnosis of doubtful cases There are tests which give an indication of deficiency of the cortisone-like hormones (or glucocorticoids), others which suggest deficiency of the mineralo-corticoids, and yet others which give at least a rough assessment of deficiency of the sex hormones None of these tests alone can establish the diagnosis, but if a deficiency of more than one of the three groups of hormones secreted by the adrenal cortex can be demonstrated, a confident diagnosis of cortical insufficiency can be made The order in which the investigations are carried out is determined by their potential danger to the Addisonian patient

Estimation of the serum level of sodium and chloride is a simple procedure, and though normal figures are quite compatible with untreated Addison's disease, low values are at least suggestive They acquire greater significance if they can be shown to be associated with a normal or high urinary excretion of sodium and chloride This point is well illustrated by the case of a young man who had been working in the engine-room of a ship in the Persian Gulf and who was admitted to hospital in Abadan as a case of heat exhaustion The physician who looked after him there first suspected that his state of salt depletion was, in fact, due to Addison's disease, when he found that the patient was passing urine with a high chloride content

The prompt and copious diuresis which normally follows the ingestion of a large quantity of fluid depends on a number of factors, one of which is an adequate supply of the adrenal glucocorticoids In Addison's disease the response to fluid administration is paradoxical, the volume of urine secreted during the night exceeding that passed during the day

The Robinson-Power-Kepler test (Fig 2) is an attempt to measure simultaneously three aspects of the impairment of renal function which accompanies cortical insufficiency, viz the poor diuretic response to water, the failure to conserve chloride, and the impaired urea clearance The formula is so arranged that the effect of these abnormalities is to reduce the numerator and increase the denominator of the fraction in each case, and so to lower the value of A If A is greater than thirty, Addison's disease is not present, if A is less than twenty-five, Addison's disease is probably present In 5 cases of Addison's disease in which we performed this test we obtained figures between five and twelve It is essentially a test of renal function and does not differentiate between primary renal disease and impaired cortical control of renal function The second interpretation can be made only if there is adequate corroborative evidence of Addison's disease

ROBINSON-POWER-KEPLER TEST OF ADRENAL CORTICAL FUNCTION

(Procedure II)

$$A = \frac{\text{Urea in urine (mg \%)}}{\text{Urea in plasma (mg \%)}} \times \frac{\text{Cl}' \text{ in plasma (mg \%)}}{\text{Cl}' \text{ in urine (mg \%)}} \times \frac{\text{Vol of ``day urine''}}{\text{Vol of night urine}}$$

Result	*Inference*
$A > 30$	Addison's Disease *not* present
$A < 25$	Addison's Disease *probably* present (if nephritis excluded)

FIG 2

A more direct assessment of the functional activity of the cortex is obtained by estimating the urinary excretion of neutral 17-ketosteroids, which reflects the level of secretion of sex hormones by the adrenal cortex (and, to a smaller extent, the testis) The excretion of less than 4 mgm of these substances in the urine in 24 hours is almost invariable in cases of Addison's disease, but the test is only specific in the negative sense that the excretion of much larger amounts makes the diagnosis untenable

In people with normal adrenal cortical function a profound fall in the level of circulating eosinophils follows the intramuscular injection of 25 mgm of anterior pituitary adrenocorticotrophic hormone (ACTH), being most marked four hours after the injection The phenomenon accompanies, and appears to depend on, an increased endogenous production of cortical hormones If no significant fall in the eosinophil count occurs, therefore, it is reasonable to infer that no functional adrenal cortical tissue exists to respond to the stimulus Our experience of this test is limited, but many American physicians, including Dr Thorn, after whom the test has been named, regard it as being very reliable

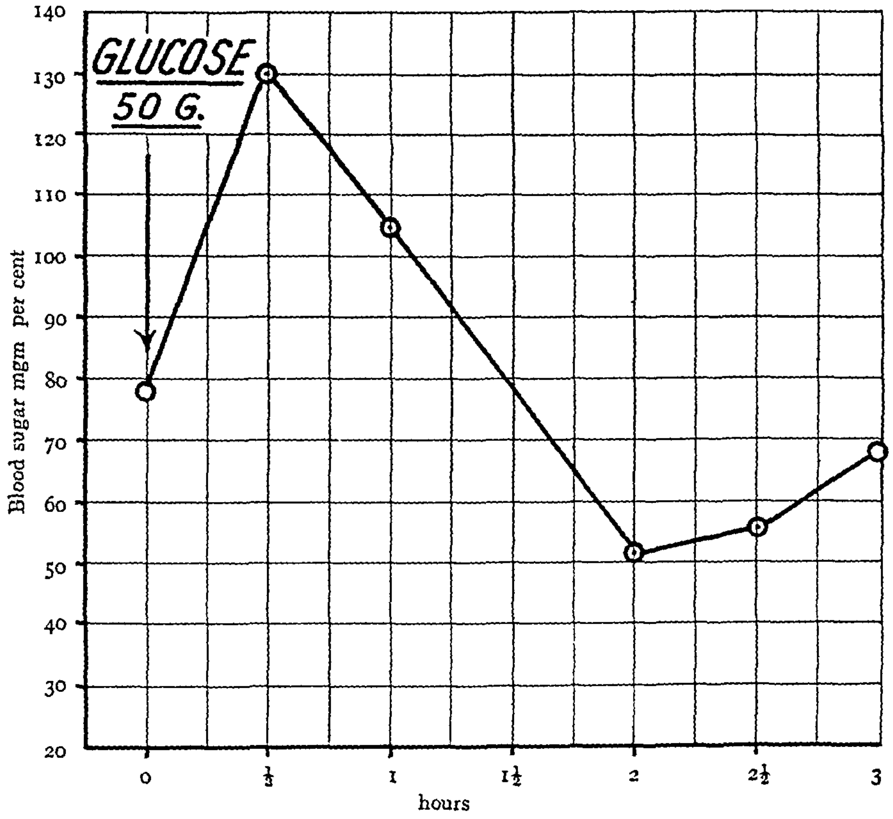

FIG 3—Oral Glucose Tolerance Test in Addison's disease (J H)

Tests which assess adrenal function by imposing a load on the cortical regulating mechanisms should only be performed in those cases in which the diagnosis remains in doubt after the simpler screening tests have been carried out The insulin sensitivity test, which is a measure of the activity of the glucocorticoids, is valuable but potentially dangerous, and should be preceded by an ordinary glucose tolerance test, which may give the same information with less hazard to the patient Fig 3 shows a typical blood sugar curve from a patient with Addison's disease Severe hypoglycæmic symptoms occurred one and a half hours after the test dose of glucose had been given, and the return of the blood sugar level to normal was delayed, indicating a deficiency of the cortisone-like hormones of the adrenal cortex which normally counter any tendency to hypoglycæmia by accelerating the mobilisation of glucose from protein Similar results are obtained in cases of Simmonds' disease and of terminal hepatic failure, so that the diagnostic value of this test also depends on its correlation with the other features of the individual case If the response to endogenous hypoglycæmia is less clear-cut, it is justifiable to carry out an insulin sensitivity test, giving a dose of not more than 0 05 of a unit of soluble insulin per Kilo of body weight by *intravenous* injection A typical response in Addison's disease is shown in Fig 4 The precipitous fall of the blood sugar level after the tiny dose of 2¼ units of insulin made it necessary to cut short the test by injecting glucose intravenously to prevent the patient from plunging into hypoglycæmic coma

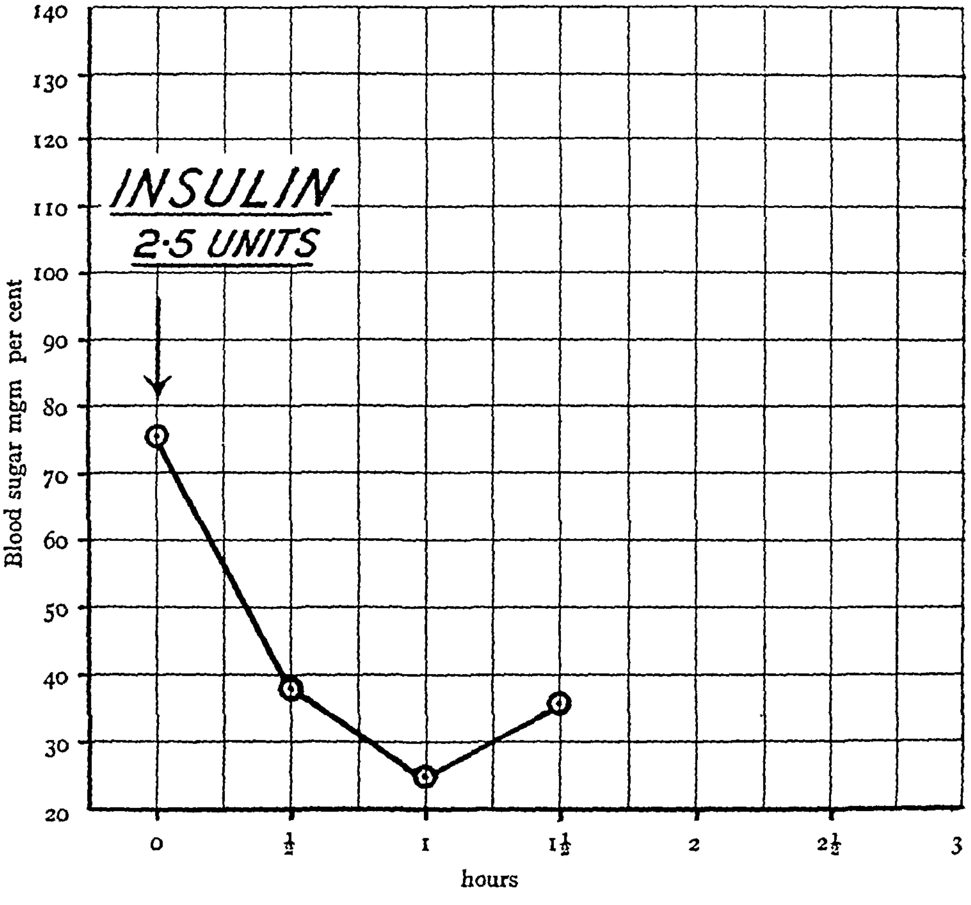

FIG 4—Intravenous Insulin Sensitivity Test in Addison's disease (J H)

The Cutler test, which consists in giving a diet low in sodium and high in potassium, and in forcing fluids, is another loading test, in this case an attempt to assess the activity of the mineralo-corticoids As the test is even more dangerous than the insulin sensitivity test, and as any untoward effects that may occur are less readily corrected, this test should never be used

It is almost certain that the symptoms of Addison's disease do not occur until total destruction or atrophy of adrenal cortical tissue has taken place, so that tests which are designed to demonstrate a minor degree of adrenal cortical deficiency have no place as diagnostic tools

In summary the diagnosis of Addison's disease can be made from the history and physical examination in the majority of cases, *once the possibility has been considered* In the remainder, the diagnosis depends on the discriminating use of a number of tests, none of which alone can give a definitive answer, with the single exception of radiological demonstration of adrenal calcification Comparison of the amount of urine passed during the day with the quantity secreted at night , estimation of the urinary 17-ketosteroids , the insulin sensitivity test, and in a few cases the Kepler test, have proved the most valuable diagnostic aids in our hands

REFERENCES

CUTLER, H H , POWER, M H , and WILDER, R M (1938), *Journ Amer med Assoc* , 111, 117

ROBINSON, F J , POWER, M H , and KEPLER, E G (1941), *Proc Staff Meetings Mayo Clinic*, 16, 37, 577

THORN, G W (1949), *The Diagnosis and Treatment of Adrenal Insufficiency*, Springfield, Illinois

THE TREATMENT OF ADDISON'S DISEASE

By C F ROLLAND, B A, M B, Ch B, M R C P Ed

If we could restore functioning adrenal cortex tissue to the patient who suffers from Addison's disease he would be cured In theory there are two ways in which such an object might be achieved First, it might be possible to stimulate the growth of any remaining shreds of adrenal cortex by the administration of the adrenocorticotrophic hormone of the anterior pituitary Unfortunately this has proved to be of no value in practice, and we must assume that Addison's disease does not develop until the glands are almost entirely destroyed Secondly, it might be possible to implant grafts of adrenal cortex This has often been done, but the results have been most disappointing and there is only one case in which this form of treatment has apparently been successful (Broster and Gardiner-Hill, 1946) In the one case of our series in which this technique was employed, a graft of hypertrophied adrenal cortex from a young man with Cushing's syndrome was implanted into the rectus abdominis muscle of a boy with Addison's disease The operation proved a double disappointment as it influenced neither the Addison's disease nor the Cushing's syndrome We must therefore conclude that Addison's disease is at present incurable and we have to rely upon replacement therapy just as we do in cases of diabetes mellitus and myxœdema

The adrenal cortex produces a considerable number of hormones, and in consequence their replacement is a complex affair Adrenocortical extracts such as Eucortone and Cortin contain most of these hormones in small quantities, but they are not very satisfactory in treatment as they are expensive and have to be injected at fairly frequent intervals They have a definite place in the treatment of Addisonian crisis but are of little value in maintenance therapy Fortunately we have two synthetic steroids, which are available in pure form and are extremely potent The first of these, deoxycortone acetate or DCA, is a member of the family of mineralocorticoids and is concerned with the regulation of electrolyte metabolism It forms the basis of ordinary maintenance therapy The second, cortisone, which is still expensive and less freely available, is an example of the so-called glucocorticoids and is primarily concerned with carbohydrate and protein metabolism and with resistance to stress We are less concerned with replacement of the various sex hormones which are produced by the adrenal cortex as they are also derived from the gonads

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Read at a meeting of the Medico-Chirurgical Society of Edinburgh on 6th February 1952

Apart from the hormones, sodium chloride can be used with effect in the correction of the disordered electrolyte metabolism and it has an established place in the treatment of Addison's disease For descriptive purposes the treatment is most conveniently divided into that of the newly diagnosed case, maintenance treatment and the management of Addisonian crisis Some American authors write about " intercritical periods " but we prefer to assume that crisis is an avoidable disaster and speak instead of " maintenance therapy "

INITIAL TREATMENT

Our object at this stage is to restore normal electrolyte and water metabolism We administer DCA by intramuscular injection and give the patient copious fluids and a daily intake of about 15 g of sodium chloride The usual dose of DCA is 5 mgm daily for the first two or three days with a gradual reduction thereafter until 1 or 2 mgm daily suffices The response is judged by relief of symptoms, an increase in weight and a rise in blood pressure Over-treatment leads to the development of œdema, hydrarthrosis and sometimes hypertension as a result of excessive retention of sodium and water In the early stages the production of œdema is common This œdema is usually mild and is generalised, often appearing first as a little puffiness of the face It is easily controlled by a diminution in the dose of DCA and the salt intake and is only dangerous if allowed to continue unrecognised The first Figure shows details of the initial treatment of a recent case It demonstrates how valuable is a daily record of the patient's weight

MAINTENANCE THERAPY

After a satisfactory initial improvement has been obtained, usually within two or three weeks of starting treatment, it is necessary to arrange for maintenance of the advantages which have been gained For this purpose we rely upon implantation of pellets of DCA into the subcutaneous fat of the anterior abdominal wall Each pellet contains 100 mgm of the hormone, and is slowly absorbed over a period of several months This technique avoids the inconvenience of frequent injections and makes a much more economical use of the steroid Various systems have been evolved by which one can estimate the required dose of the implant These depend upon making an assessment of the minimum satisfactory daily dose by intramuscular injection and may take a long time In our experience with 21 cases who have received a total of 115 implants we find that 300 or 400 mgm is satisfactory in the great majority Only twice have we given 500 mgm If we are in doubt we give 300 mgm , because it is always easier to add another pellet at a later date than to remove one or two pellets from the abdominal wall

The technique of implantation is simple and the operation causes less inconvenience to the patient than the extraction of a tooth After preparation the skin is anæsthetised with 1 per cent procaine and an incision of 1-2 cm in length is made Tunnels are then made in the subcutaneous fat by blunt dissection with artery forceps The object is to place the pellets about 4-5 cm from the incision and each well apart from its neighbours The pellets are fragile and must be handled delicately, for if they break they are absorbed more rapidly We insert the pellets through a special cannula with a blunt trocar and find that this instrument makes the operation much more easy In the past three years only one pellet has been extruded through the incision The little wound is closed with one or two fine nylon sutures

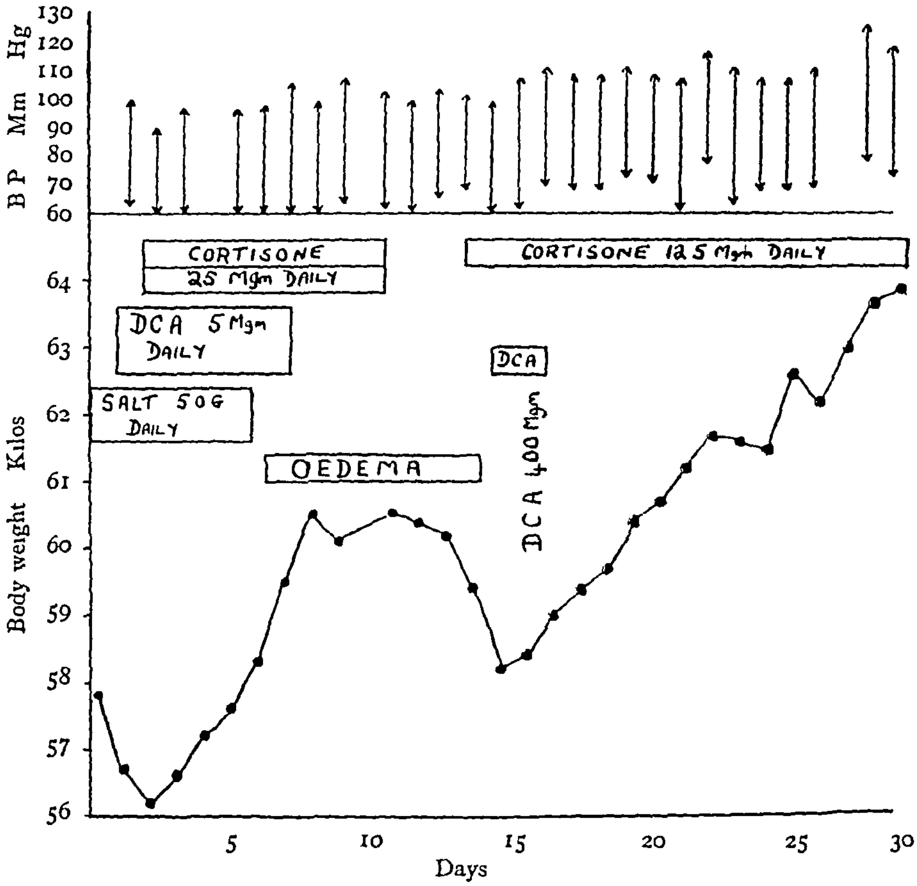

FIG 1 —Addison's disease Initial treatment *J S*

In maintenance therapy we use sodium chloride as a counterbalance to the DCA When the hormone is being absorbed rapidly in the first few weeks after implantation, it is common to find a little œdema, hydrarthrosis and hypertension When these signs of over-treatment appear we advise the patient to avoid all salt other than that used in cooking Later, when absorption is much slower we advise free use of table salt and sometimes even prescribe up to 5 g of sodium chloride daily in tablets in addition to the normal dietary intake

In deciding when another implant is necessary we pay attention to the patient's symptoms, to his weight and his blood pressure When these factors indicate that treatment is inadequate we make a further implant It is seldom necessary to admit the patient to hospital for this purpose In our experience we find that the average interval between implants is about seven months After three implants have been made we have a more definite knowledge of how long it takes the individual patient to absorb his pellets, and we then prefer to arrange a new implant by reference to the calendar rather than by waiting for a partial relapse to occur before renewing the store of DCA

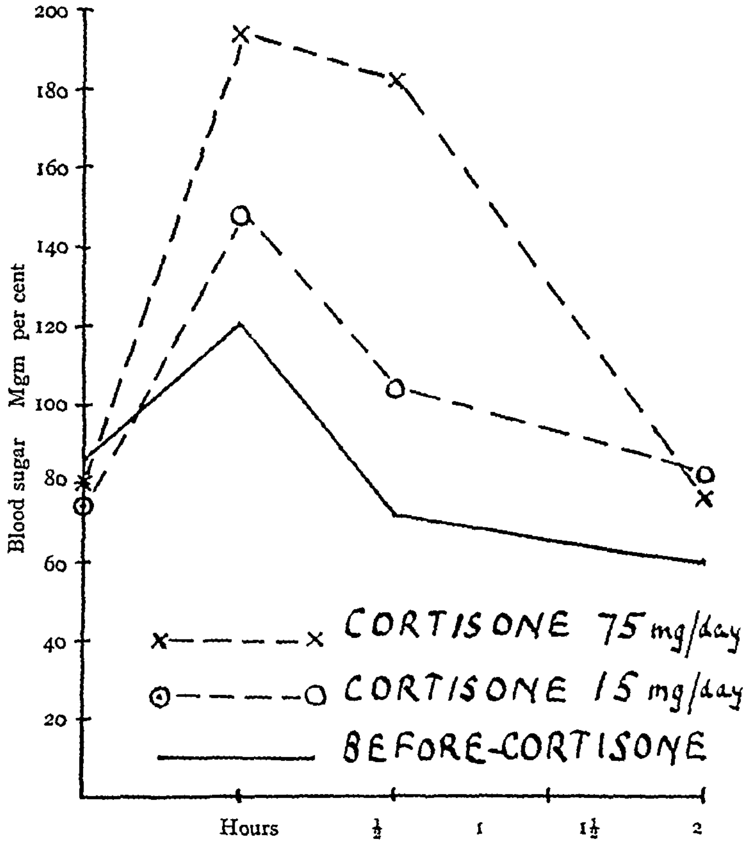

FIG 2 —Oral glucose tolerance tests in Addison's disease (E B)

Satisfactory though it may be, treatment with DCA and salt does nothing to correct the tendency to hypoglycæmia which is responsible for much of the tiredness in Addison's disease Supplementary treatment with cortisone does much to remedy this situation by preventing hypoglycæmia and, though this is less easy to measure, it probably improves resistance to stress and infection We have had no experience with the implantation of pellets of cortisone but we find that 12 5 to 25 mgm by mouth or intramuscular injection is a satisfactory daily dose Fig 2 shows blood sugar curves in one patient, and compares that done when she had no cortisone with those done when she was having 75 and 15 mgm daily

ADDISONIAN CRISIS

In maintenance therapy it is our first duty to protect the patient from this disastrous complication, which, if it is not fatal, leaves the patient and the physician exhausted after a prolonged struggle for life Crisis is precipitated by two things first, a failure to maintain adequate replacement therapy , and second, by exposure of the patient to a stress, to cope with which he is inadequately equipped Such stresses are acute infections, treatment with opiates, surgery and in a recent case an attack of migraine Prevention of crisis depends upon avoidance, or suitable management of the precipitating factors

When crisis does develop, early treatment is of the greatest importance and, as in diabetic coma, each case demands individual management No routine or rule of thumb method can be laid down The main tasks are to correct dehydration, to restore lost sodium and to combat hypoglycæmia We give large amounts of a 6 per cent glucose solution in normal saline by intravenous infusion and we give large doses of DCA and cortisone by intramuscular injection to enable the patient to make proper use of the water, glucose and sodium which he receives It may be necessary to give as much as 30 mgm of DCA and 300 mgm of cortisone in the first 24 hours We judge the response by the general condition of the patient, his pulse, temperature, blood pressure and urinary output, and we have to avoid the production of œdema by over-treatment In extreme emergencies the intravenous injection of 10 to 30 ml of an aqueous adrenocortical extract, such as Eucortone, may be a life-saving measure When cortisone is not available we give such an extract by intravenous or intramuscular injection at intervals of 3 to 4 hours until the patient is better The following table shows the total quantities of the various substances which were administered to a patient during two days of Addisonian crisis from which she recovered

ADDISONIAN CRISIS

A D , female, aged 39 No previous treatment Crisis precipitated by migraine During 48 hours she received —

Intravenous infusion	Water	6 litres
	Sodium	42 g
	Glucose	280 g
Cortisone acetate		425 mgm
Deoxycortone acetate		20 mgm
Eucortone		20 ml

We find that many patients in Addisonian crisis have a high temperature, and this may make it difficult to decide whether or not there is an acute infection If there is any doubt on this point we give large doses of a suitable antibiotic such as penicillin or streptomycin, for it is useless to treat the crisis and ignore a possible cause While we have a very limited experience of the use of cortisone in crisis we feel that it is of great value in limiting the period of the emergency Success in the treatment of Addisonian crisis depends upon the constant attendance of the physician and his readiness to deal with the rapidly changing situation

REFERENCE

BROSTER, L R, and GARDINER-HILL, H (1946), " Addison's disease Treated by a Graft," *Brit Med Journ*, 2, 570

PROGNOSIS IN ADDISON'S DISEASE

By J D MATTHEWS, B A, M B, Ch B, M R C P Ed

THE story of the prognosis in Addison's disease falls into easily defined eras, dating from those landmarks in history when each new therapeutic measure was introduced

The first era, from the time in 1849 when Thomas Addison first described the disease so accurately, until 1930, was a long period when attempts at treatment were all in vain, and the majority of sufferers died within a year of the onset of the malady

In 1930, a potent cortical extract, prepared by Swingle and Pfiffner, was introduced for the first time, and it was found to be of great value in the management of Addisonian crisis With the emphasis which Loeb placed on the value of salt in maintenance treatment, this period can be called the era of cortical extract and salt

However, in Edinburgh between 1930 and 1938, a study of 30 cases by Dryerre showed no great improvement in prognosis in spite of the introduction of these new measures Twenty-three of his cases had died within six months of diagnosis, and only 4 survived longer than two years The reasons for this high mortality rate at that time probably lie in the facts that adequate supplies of cortical extract were not always obtainable, its cost was very high, and it is doubtful too if adequate doses were administered during a crisis

The third era is that of deoxycortone acetate which was synthesised by Steiger and Reichstein in 1937 During the early years of its use DCA was also in short supply, but it was used whenever possible from 1939 onwards In that year here in Edinburgh one of the first patients in the country received an implant of DCA pellets For purposes of comparison then, it seems justifiable to regard the years from 1939 to 1951 as the third or DCA era, and the change in

Mortality in 60 Cases of Addison's Disease

Years of Survival	1930 1938 (30 cases)		1939 1951 (30 cases 1 unknown)	
	Alive	Dead	Alive	Dead
1	1	23	4	10
2		2		
3	1	3	4	1
4			1	
5				
6			1	3
7			1	1
8				1
9				
10			1	
11			1	

Read at a meeting of the Medico-Chirurgical Society of Edinburgh on 6th February 1952 prognosis since 1939 compared to the previous period is quite striking

The table represents the mortality and years of survival in 60 patients with Addison's disease The left-hand column refers to the years of survival from the time when the diagnosis was first made in each case The 60 cases are divided into two groups by the double set of vertical lines, showing Dryerre's 30 cases from 1930 to 1938 on the left, and the 30 cases in Professor Dunlop's charge from 1939 to 1951, (corresponding to the DCA era) on the right The position of each patient has been assessed as to whether alive or dead in the last year of each period, a case being placed in the alive or dead column of each group but not in both Of Dryerre's cases, in 1938 there were only 2 living, one of whom had lived one year and the other 3 years The rest of the 30 were dead in 1938 and 23 had died within a year of diagnosis Of the others who were dead, 2 had lived two years and 3 survived three years

In the DCA era at the end of 1951 the position is very different Thirteen are living, 4 of whom were diagnosed within the last year Sixteen were dead in 1951 Counting up all those, alive or dead, who have lived longer than two years since 1939 the total is 15, which compares very favourably with only 4 alive after two years in the previous era Counting up those who have lived longer than five years there are 9 in the 1939-51 series, whereas no case of Addison's disease ever attained that life span previously In the DCA era there is still apparently a high mortality in the first year Ten are recorded but these 10 patients could not or did not receive adequate treatment Five were moribund when first seen or were in the last stages of tuberculous or carcinomatous disease These are inevitable Two of the others, however, occurred in 1939 when there was not enough DCA available for their treatment, and the remaining 3 failed to report when requested to do so It seems then that half of these early deaths in the first year are preventable by adequate maintenance care

The advance in this third era is probably not entirely due to DCA A more profound knowledge of the use of cortical extract and intravenous fluid in crisis, and regular supervision of these patients have also played a part Obviously, however, there is still room for improvement in prognosis, not only from the point of view of mortality, but also with regard to the capacity of these patients for work A survey of our 30 cases shows that half were never able to work, and the others though usefully employed have been unable to perform tasks involving much physical exertion

The main factors which adversely affect the prognosis are those which precipitate Addisonian crisis, and have already been mentioned It is now common knowledge that these patients are extremely sensitive to morphine and all anæsthetic drugs, and we know too that starvation will produce hypoglycæmia and even coma It is intercurrent infection that we regard as the common and most important cause of acute adrenal insufficiency Moreover, such a catastrophe may occur, as on two recent occasions, within only a week or two of re-implantation of DCA In particular, upper respiratory infection has been responsible on at least ten different occasions in our patients and four of them were associated with a streptococcal infection of the throat which seems to cause deterioration with great rapidity An infection, which is by no means the least in importance, is active tuberculosis We believe it has induced a critical lapse on six different occasions, being miliary spread in two cases, pleural effusion, active pulmonary phthisis, caries of the spine, and abdominal tuberculosis in one case each There is no doubt that progressive tuberculosis elsewhere in the body, though possibly in the adrenal glands as well, makes the prognosis more gloomy, and it is noteworthy that the two patients who have lived longest in our series show no clinical evidence of tuberculous disease Sixty per cent of our cases have suffered from tuberculosis in some form, though we can only find evidence of it in the adrenals in 36 per cent It is of interest that in one case at autopsy there was evidence of pulmonary tuberculosis with no tuberculous disease in the adrenals, which had merely undergone simple atrophy, so that the finding of pulmonary tuberculosis does not necessarily imply a tuberculous ætiology to the Addison's disease, though it undoubtedly affects the prognosis adversely

In fact modern treatment is already solving many of these problems Not many years ago Addisonian crisis was usually fatal and miliary tuberculosis invariably so, and yet recently, with the co-operation of Professor Cameron's staff, we were able to produce a quite remarkable recovery in a girl with Addison's disease who had both these major catastrophes The treatment in this case was, of course, with streptomycin, DCA and cortisone From our records, too, it is plain that an appreciation of the management of crisis is yielding good results, for in the past five years we have had only one death out of 12 incidents of crisis, and it should be mentioned that much of our understanding of treatment is due to Dr J B Donald who worked under Professor Dunlop until 1949 Even pregnancy is becoming safe, for last year we were able to conduct a young woman with Addison's disease to term and through a normal and successful labour, with the help of Professor Kellar's staff Again cortisone as well as DCA was given as replacement therapy This is the second pregnancy that has been encountered in this series

A crisis due to failure to reimplant soon enough should not now occur, and we have found that a regular monthly visit to a hospital where a special interest is taken in the disease is valuable in helping to assess when a further implant should be done Outside hospital we are fortunate in obtaining the interest and co-operation of the general practitioners in the care of their patients During minor infections, such as coryza, we recommend supplementary injections of 5 mgm DCA every other day If the slightest change in the patient's subjective feeling occurs, it is regarded seriously, and in particular we have found that abdominal pain and vomiting are grave features which herald a crisis and demand immediate attention as quickly as any surgical emergency Should such warning signs occur, and especially if intercurrent infection is present, the practitioner is encouraged to give 25 mgm cortisone (if available), 5 mgm DCA and 500,000 units of crystalline penicillin, all by intramuscular injection, and then arrange admission to hospital without delay

It is apparent that we are now witnessing the dawn of a new era, a fourth era, in the management and prognosis of Addison's disease It may be called the cortisone and DCA era From our dealings with crises relieved dramatically by cortisone, and from our limited experience of the drug in maintenance treatment, we are convinced that the future lot of these patients will be a happier one, for there is no doubt that cortisone can relieve hypoglycæmia and enable the patient to resist infection more readily We hope that in the not too distant future enough cortisone will be available for maintenance purposes, when it may be given orally or by implantation It should, however, be emphasised again that cortisone does not supersede DCA and that both are required for adequate replacement therapy

In conclusion, and in order perhaps to keep our study of a rare disease in proper perspective, I should add that the major problem of this disease is really only a very small part of the much wider problem of the prevention of tuberculosis, and thereby many cases of Addison's disease will be prevented With advances in this field, the Addisonian patient will in the course of time become an even rarer phenomenon

REFERENCES

DRYERRE, H W (1938), *A Survey of the Therapy in Addison's Disease*, Gunning Victoria Prize, University of Edinburgh

DRYERRE, H W (1939), *Brit Med Journ*, 1st May, p 971

LOEB, R F, ATCHLEY, D W, STAHL, J (1935), *Journ Amer Med Assoc*, 104, 2149

ROWNTREE, L G, GREENE, C H, SWINGLE, W W, and PFIFFNER, J J (1931), *Journ Amer Med Assoc*, 96, 231

STIFGER, M, and REICHSTEIN, T (1937), *Nature*, 139, 926

DISCUSSION

Dr Batty, opening the discussion, stated that by the time the patient reported with Addison's disease the diagnosis could be made without special test Occasionally difficulty was encountered with the hypotensive psychiatric casualty, but such a case could be correctly assessed if pains were taken in obtaining a good history and making thorough clinical examination

The speakers and the literature have given the impression that the manifestations of over-dosage with DCA occur simultaneously In some of his cases Dr Batty had noticed that œdema or hypertension occurred alone, and at the present time he had a patient under treatment with blood pressure 180/110 mm Hg without œdema or significant change in weight

The speed with which a patient could pass out of control when a DCA implant was used up was sometimes impressive, and he preferred symptoms rather than laboratory tests as indications for further implantation therapy

Professor Dunlop pointed out that Addison's disease was not quite as rare as some people supposed During the last fifteen years he had had fifty-eight cases in his wards Of those which had come to post-mortem the great majority had been found to be due to tuberculosis and only a very few to idiopathic atrophy of the suprarenals One had been due to carcinoma and one was possibly syphilitic in origin

As regards diagnosis he agreed with the speakers that most cases could be diagnosed quite easily on purely clinical grounds and without any elaborate investigations provided the possibility of the condition was kept in mind A few cases, however, presented a very difficult diagnostic problem The diagnostic tests he had found most useful were the X-ray of the suprarenal region for possible evidence of calcification, the glucose tolerance test, the insulin sensitivity test and the estimation of the 17 ketosteroid excretion in the urine Cutler's test was dangerous and should not be attempted

Till recently in spite of DCA and salt the lives of patients suffering from Addison's disease had always been most precarious owing to their extreme sensitivity to any form of noxious stress With the addition of cortisone to our armamentarium we were now entering a new therapeutic era in which the prognosis might be very different, since a more complete replacement therapy would be possible by combining DCA with cortisone

In his view the most valuable single prognostic test was the regular weighing of the patient, and he made a plea for the installation of efficient weighing machines in hospital wards since accurate weight records were frequently neglected in clinical medicine generally in favour of more recondite investigations and were often of much more importance

Dr Loraine referred to his recent experiences in Dr Thorn's and Dr Albright's Clinics in Boston, where cortisone is used in all cases of Addison's disease In the opinion of Dr Albright, cortisone relieves hypoglycæmia, improves the appetite and prevents some of the depressive symptoms He wondered if Dr Rolland had encountered psychoses in any of the patients with Addison's disease receiving cortisone Out of fourteen patients with Addison's disease recently treated by Dr Albright, mild psychotic symptoms had been noted in three

The dosage given in the clinics in Boston was usually 12½ mg /day by the oral route During pregnancy additional quantities of cortisone are required

Dr Loraine also agreed that the clinical approach was the best method of diagnosis, but was of the opinion, that laboratory tests were of considerable value in a small proportion of cases Many tests of adrenal function are employed in the various endocrine clinics in the U S Four-hour and 48-hour ACTH tests are widely used along with urinary 17-ketosteroid and 11-oxysteroid estimations The water test, originally described by Kepler, is also a valuable index of adrenal activity Little reliance is now placed on eosinophil counts alone, as results are too variable from patient to patient to be of much significance The adrenaline test introduced by Thorn and his co-workers in 1948 and depending on the reduction of circulating eosinophils after the administration of the hormone, is no longer used Thorn's group have themselves demonstrated that adrenaline is capable of causing an eosinophil depression in totally adrenalectomised patients Recently, Dr Nelson and Dr Samuels of Salt Lake City have introduced a chemical method of assay of 17-hydroxy-corticoids in human peripheral blood In normal patients concentration of the 17-hydroxy corticoids lay between 4 and 10 γ 100 ml of blood Abnormally high levels were noted in Cushing's Syndrome and also after the administration of I V ACTH Zero levels were encountered

Dr Kinnear, replying, said that it was encouraging to hear from Dr Lorraine that methods for assaying corticoids in human blood were now being worked out in the United States Such tests would give a much more accurate assessment of adrenal function than was possible with those now available The present tests were non-specific, measuring renal function or carbohydrate metabolism, both of which were controlled by many factors apart from the adrenal cortex

With regard to pigmentation occurring in the mouth in conditions other than Addison's disease, Dr Kinnear said his experience in this respect was limited to three cases—one was a patient who had a Negro ancestry, the second was an ephedrine addict, and the third was a healthy man with buccal pigmentation and no other abnormality

Dr Rolland, in reply to Dr Batty's remarks on hypertension, said that in some patients it had appeared as the only sign of over-treatment, but these patients often felt better when they were hypertensive and he felt that if they had not had Addison's disease they might well have had essential hypertension It was because deterioration might occur suddenly when the implant had been absorbed that it was found advisable to make a new implant with reference to the calendar rather than by waiting for a relapse to occur

He was interested to hear that psychosis had been observed in patients with Addison's disease treated with cortisone and remarked that his experience had been to the contrary, in that these patients had usually become a little euphoric, pleasant and co-operative

In answer to Professor Dott, Dr Rolland said he was very interested in the treatment of hypopituitarism but felt that it was better to attempt to stimulate the patient's own adrenal cortex by administering ACTH If this was not available, cortisone was certainly of great value and could be supplemented with DCA He had seen cases in which DCA caused a rapid retention of salt and water and had the impression that it was safer in this respect if it was given to patients who had been taking thyroid

In reply to Dr Elias-Jones he agreed that there was abundant evidence, in man as well as animals, that cortisone had an adverse effect upon tuberculosis, but he emphasised that this occurred when large doses were given and was not seen with the much smaller doses that were necessary for replacement therapy in Addison's disease

Dr Matthews, in his reply, answered questions about the case of pregnancy in Addison's disease It had been found that the requirements of DCA diminished during the course of the pregnancy and the patient required very little during the last two or three months This was probably due to the increased production of endogenous sex hormones which have some salt-retaining properties and in this sense the patient might be said to have improved temporarily with regard to her Addison's disease The baby in this case was well in all respects and showed no evidence of cortical dysfunction With regard to the comments by the President on the incidence of Addison's disease, Dr Matthews drew attention to Dr Thorn's series of over 150 cases, collected from a wide area in the United States with a vast population, and he compared this number with the present series of 30 cases collected over a similar period from a much smaller population in South-East Scotland It might be inferred from this that Addison's disease is comparatively more common in Scotland, possibly due to the high incidence of tuberculosis in this country

THE DIAGNOSIS OF JAUNDICE

By C F W ILLINGWORTH, Ch M , F R C S Ed

JAUNDICE is not a disease but a symptom, which may develop as the result of many diverse pathological processes It is possible to enumerate over fifty possible causes of jaundice, but fortunately in the great majority there are other and often more clamant symptoms which quickly afford a diagnosis The jaundice which occurs in severe infections, or in severe hæmolytic processes, or in specific diseases such as Weil's disease, needs no special discussion For practical purposes we are concerned with the common diseases in which jaundice is the main, or one of the main, clinical features

To afford a basis for this discussion I have analysed the records of jaundiced cases admitted to the Western Infirmary, Glasgow, during the five-year period 1946-50, excluding only those in which the jaundice was of shorter duration than two weeks I cannot claim that every case has been included, for our records are classified under diseases, not symptoms, and a few cases may have evaded my quite lengthy search , but at least the series should give us an idea of the main types of case we have to deal with

There were altogether 271 patients, whose ages ranged from 18 to 81 I have classified them into four groups

1	Hepatogenous jaundice, including various types of acute and chronic hepatitis	101 cases
2	Neoplastic jaundice, including carcinoma of the pancreas, bile ducts and gallbladder, and metastases from other sources	97 ,,
3	Stones in the common bile duct	39 ,,
4	A group of miscellaneous conditions such as pancreatitis and stricture of the ducts, and cases of undetermined nature	34 ,,

It will be seen that the two large groups, hepatogenous and neoplastic are almost equal, each accounting for over a third of the total, while stones in the common duct came next with almost a seventh of the total Expressed in a different way, cases of purely medical interest and mainly surgical interest were almost equally balanced

But a classification such as this is of little value unless we take into account the age incidence of these different diseases It is common knowledge that the various forms of hepatogenous jaundice are most frequent in the young, while jaundice due to gallstones and to carcinoma usually affects older people

In my series, the age of forty marks a critical point, for up till then, practically every case has been hepatogenous, while after that point stones and carcinoma become increasingly more common If, therefore, we exclude the younger patients a totally different pattern of incidence

Read at a Joint meeting of the Medico Chirurgical Societies of Edinburgh and Glasgow in Edinburgh on 23rd November 1951 emerges, for now the proportion of cases due to hepatitis has shrunk to barely a quarter, while stones and malignant disease account for nearly two-thirds If we pursue the same theme in patients over 60 years of age, we find that now stones and malignant disease account for almost three-quarters, while hepatitis has shrunk to one-sixth

Clearly these figures have an important significance in our clinical approach, for whereas in younger patients we can safely assume that the jaundice is hepatogenous, in older patients we must increasingly turn our thoughts in the direction of the surgical diseases

HEPATOGENOUS JAUNDICE

Acute hepatitis may occur in epidemic form or be transmitted by syringe or in transfused blood, or it may be due to liver damage by many chemical poisons or by toxins of unknown character It may take a mild or severe form The diagnosis is most difficult in elderly persons in whom, if the prodromal phase is atypical or the course prolonged, the picture may simulate malignant disease A common error is to place too much reliance on the history of exposure to risk Thus carcinoma developing in a chemical worker, in a patient who has undergone injection treatment or one who has been in contact with epidemic cases is apt to be misdiagnosed as hepatitis

CALCULOUS JAUNDICE

Of the two common surgical types of jaundice, that due to gallstones is usually unmistakable, and indeed there are few diseases in which the underlying pathology is more accurately reflected in the clinical symptoms The long history of dyspepsia and recurring pain while the stone lies in the gallbladder, the acute colics that mark its passage to the duct, and finally the intermittent or fluctuant jaundice of a ball valve obstruction provide evidence which is usually quite beyond doubt

There are exceptions, however, and indeed in a personal series of 73 cases I have met with 14 atypical examples, and these can only be appreciated if we understand the possible modifications of the underlying pathological process Thus, sometimes if the cystic duct is of wide bore a small stone may slip down without acute colics Sometimes the stone on reaching the duct leads to cholangitis with upward spread of infection to the liver and with symptoms such as pyrexia, rigors, and severe toxæmia which may lead one to attribute the jaundice to a toxic cause Sometimes, lastly, though this is rare, a stone reaching the common duct may impact tightly, causing jaundice which progressively deepens I have had two such cases in which the painless progressive jaundice was thought to be due to carcinoma

NEOPLASTIC JAUNDICE

In this category we include primary cancer of the pancreas, ducts or gallbladder and secondary growths from various other sources

Their relative frequency in our hospital practice is indicated in the Table

TABLE

Neoplastic Jaundice

Type	No of Cases
Carcinoma of pancreas	44
Carcinoma of ampulla	11
Carcinoma of common duct	7
Carcinoma of gall bladder	16
Metastatic growths	19
Total neoplasms	97

Secondary growths require little consideration Often the jaundice comes late in a patient who is obviously cachetic Sometimes there is palpable nodular enlargement of the liver with ascites and perhaps secondary nodules elsewhere, while the primary focus may be evident on clinical or radiological examination

Carcinoma of the gallbladder is much commoner than is usually recognised It is almost always associated with gallstones, so the clinical picture is a mixed one The patient, almost always a woman, gives a long history of recurring biliary pain and dyspepsia The growth itself is generally symptomless until it encroaches on the common duct or penetrates deeply into the liver, when jaundice appears insidiously and without pain Often by this time the growth is of large size and can be palpated

Primary carcinoma of the pancreas and bile ducts, which for convenience we may take together, form the largest group in this category

In recent years this type of malignant disease has assumed a new importance in view of developments in surgical treatment Formerly inoperable, or at best palliated by short circuiting operations which did little to prolong life, they are now amenable to early radical removal In my own personal experience of 60 cases seen during the past ten years there have been 20 in which the radical operation has been practicable This new outlook makes it much more important now than in the past to arrive at an early diagnosis In particular, we must pay special attention to the group of periampullary carcinomas, for a growth in this situation progresses slowly and metastasises late, so radical removal is not only more often possible but more often likely to be successful

The classical features of jaundice due to carcinoma of the pancreas are well known, its insidious origin, early or late according as the growth originates near to or far away from the duct, its steady progress and ultimately deep olive green hue Well known, too, are some of the fallacies of orthodox teaching For example, we now recognise that far from being a painless disease, carcinoma of the pancreas gives rise to pain in well nigh 50 per cent of cases, not the colicky pains of gallstones but a dull ache over the liver, probably due to distension of the whole bile duct system We recognise also that while, as Courvoisier pointed out, the gallbladder is nearly always distended it may be out of reach deep under cover of the enlarged liver, so failure to palpate it by no means invalidates the diagnosis

In periampullary carcinoma since the growth originates close to the bile duct jaundice often appears very early in the course of the disease and it might be supposed that for this reason the diagnosis would be reached at an early stage Unfortunately, in quite a large proportion of such cases, the diagnosis is obscured by a most misleading feature, namely that the jaundice instead of following the usuaul persistent, progressive course, tends to fade after a week or two and may disappear completely, only to return again after the lapse of a further period of a few weeks Probably this feature can be ascribed to ulceration of the growth, which then relaxes its grip of the bile duct It is most misleading, for only too often when the early jaundice fades, both patient and doctor, greatly relieved, are happy to ascribe it to a " catarrh " or a " chill on the liver," and this false diagnosis is retained long after the jaundice has reappeared Some of my most benign and therapeutically most hopeful cases have thus been ascribed to hepatitis and effective treatment delayed too long

Thirdly, in a small proportion of ampullary growths, the picture is altered by infection spreading from the ulcerated growth to the duct and liver Here again the pyrexia and chills and toxæmia may obscure the diagnosis and delay the treatment

LABORATORY INVESTIGATIONS

The time at my disposal is too short to permit even a cursory survey of the multitude of laboratory investigations which from time to time have been recommended as aids to the diagnosis of jaundice It will suffice to say that none is consistently reliable and all must be interpreted in the light of the varying pattern of behaviour of the underlying disease processes

X-ray examination is of limited value Occasionally a straight X-ray will demonstrate a stone in the line of the common duct Cholecystography is quite useless, for a liver that cannot excrete bile certainly will not be able to excrete the opaque dye A barium meal may demonstrate malignant deformity of the duodenum but only in late, inoperable stages

In carcinoma of the pancreas analysis of the fæcal fats might be expected to be of value, but this is only rarely so—perhaps because the retained pancreatic juice often finds its way through anastomosing channels into the accessory duct of Santorini

The value of liver function tests will be discussed in a later paper and I shall not try to anticipate its findings Theoretically these tests should distinguish between hepatitis, where the liver function might be expected to be reduced, and obstructive jaundice where, at least in the early stages, it should be unimpaired , but in practice the results are less clear-cut and not consistently reliable

Aspiration biopsy of the liver can be relied upon, in skilled hands, to provide a key to the diagnosis in many cases, but there is a risk of intraperitoneal hæmorrhage which may be painful, alarming and even, though rarely, fatal

But we have at our disposal one method of investigation which is consistently reliable, the diagnostic laparotomy Before considering the place it should occupy, let us pause to review the problem as it presents itself to us so often in practice

We are all familiar with this problem, the patient over 40 or more especially over 50, well until recently or with a brief history of rather vague ill health, who then gradually becomes jaundiced Questioning elicits no relevant fact in the previous history while examination reveals no relevant sign except the jaundice itself and the consequent changes in pigmentation of the urine and fæces

We have to ask ourselves whether we are dealing with a rather atypical example of hepatitis or a case of malignant obstruction to the bile ducts

At this stage it is important to recognise clearly the limitations and objectives of the art of diagnosis In practical medicine, diagnosis is not an academic science but the handmaiden of therapeutics The main question we have to decide is whether to treat our patient conservatively or by operation and while it is gratifying to be able to make an exact diagnosis such precision is often neither possible nor necessary

Moreover we have to make our decision in time to benefit the patient, and here it must be recognised that even a short delay is harmful, for with persistent jaundice the dangers of a major intervention increase progressively For this reason any prolonged investigation should be avoided Indeed in my view a time limit should be set in every case, say one week from the first consultation, by which time the decision as to treatment should be possible

In making this decision we have to bear in mind two important considerations First we have to remember that in the type of case under discussion, the older patient with jaundice of obscure causation, there is a three-to-one or even a four-to-one probability of malignancy and in that event the only prospect of cure is by early operation at the hands of a surgeon competent to undertake such a task

In the second place we have to recognise that the operative exposure *per se* is no longer a serious matter, even in the deeply jaundiced patient Formerly, to open the abdomen in a patient with jaundice was to court disaster, either from hæmorrhage or from liver failure, but in recent years the use of vitamin K and improvements in anæsthesia and post-operative care have transformed the position so that now an exploratory laparotomy in jaundice carries no special risk

In view of these considerations, indeed, I submit that we should change our whole approach to treatment In the past, quite properly, our aim was to operate only when the indications were clear, now the risk is so much less and the prospect of benefit so much greater, we should favour recourse to surgery much more readily than in the past

THE DIAGNOSIS OF JAUNDICE

By JOHN BRUCE, C B E , M B , F R C S Ed

FEW problems in clinical diagnosis carry so much responsibility, or impose so serious an obligation, alike on practitioner, physician and surgeon, as that of jaundice The last quarter-century has witnessed important accretions in our knowledge of the liver in health and disease , the mechanisms which lead to the accumulation of bile pigment in the blood are, for the most part, well understood , and a whole battery of biochemical tests is now available to the clinician. Nevertheless, the application of such advances to the individual case of jaundice may provide an unsatisfying exercise at those very times when an accurate and speedy answer is most desirable

PATHOLOGICAL BASIS OF JAUNDICE

The pathological states that may give rise to jaundice are many , but, broadly speaking, they operate to produce jaundice in one of two ways—by retention of bile pigments in the circulation (*retention jaundice*), or by their passage back into the blood stream from the liver (*regurgitation jaundice*) Not perhaps as happily designated as they might be, the features of retention and of regurgitation jaundice are sufficiently distinctive to permit of their easy differentiation when they are encountered in their pure forms

In *retention jaundice* the fundamental error is a surfeit of pigment in the blood in consequence of an increase in the amount or the rate of red blood cell destruction The liver deals with as much of the excess as it can, but there is an unused surplus which has to be " retained " in the circulation The coarse molecular structure of this crude pigment denies it excretion by the renal filter, and so bile is absent from the urine, a convenient and easy diagnostic criterion

Uncomplicated retention jaundice seldom gives rise to diagnostic difficulty, and for the purpose of this discussion, it may be neglected It is the second of the broad classes of jaundice that so often leads to perplexity In essence, *regurgitation jaundice* implies the presence in the blood stream of bile which has already been elaborated by the liver cells, and for one reason or another, has failed to reach the intestine in normal quantity , but since the bilirubin in its passage through the liver cells has been altered, probably in respect of its molecular size, it can now pass the renal filter and appear in the urine Choluria and a quantitative variation in the intestinal flow of bile thus provide the simplest evidences of " regurgitation " jaundice

Read at a joint meeting of the Medico-Chirurgical Societies of Edinburgh and Glasgow in Edinburgh on 23rd November 1951

Bile may be forced back into the circulation under varying circumstances, indeed, the accident is common both to the jaundice of extrahepatic biliary obstruction (*obstructive jaundice*) and to that of the severer grades of acute and chronic disease of the liver (*hepatogenous* or *toxic and infective jaundice*)

In the extrahepatic obstructions, the mechanism is probably by rupture of the distended intercellular bile canaliculi directly into the veins, or possibly, into the hepatic tissue spaces, from which it reaches the circulation by lymphatic channels In the several varieties of hepatitis, the mechanics are less clear, the shrinkage of the necrosed liver cells may allow the bile to seep out into the tissue spaces, and thence by way of the lymphatics to the blood stream, or a true intrahepatic obstruction may be established, if the liver cholangioles become temporarily blocked by œdema or by the accumulation of inflammatory products in the acute inflammations, or permanently occluded by fibrous tissue, or distorted by the pattern of the regenerating nodules, in the healing and the healed phases of hepatitis

The differentiation of the obstructive and the hepatic types of regurgitant jaundice is important both in relation to treatment and to prognosis, for, whereas arrest of the regurgitation in those varieties of icterus due to disease of the liver parenchyma must be spontaneous, and in consequence of the resolution and natural cure of the disease, the jaundice of the extrahepatic obstructions can be relieved permanently only by surgical attack on the obstructive lesion

Such, in brief, is the pathological background of "regurgitation" jaundice It makes clear why the icterus of the acute liver necroses, of the intrahepatic canalicular occlusions of the cirrhotic liver, and of such extrahepatic obstructions as stone in the common bile duct, are fundamentally so similar, with bile in the urine, with a variable diminution in the fæcal biliary content, and with essentially comparable changes in the pigment content of the blood It emphasises too, that the crux of the practical diagnostic problem of jaundice is to identify those patients with extrahepatic obstructions demanding surgical intervention, by the scrutiny of such other evidence as we can assemble In effect, this implies in each case of jaundice a scrupulous search for unequivocal signs of disease outwith the liver or, alternatively, the accurate demonstration of a disorder of the liver parenchyma, and all the knowledge, the judgment, and even the intuition of the clinician may be required to establish a diagnosis in reasonable time

The time factor deserves the strongest emphasis, since delay in coming to a decision may gravely jeopardise the results of surgery There is no doubt, for example, that the mortality attending the removal of the simple calculous gallbladder is trifling, but when stones have invaded the common bile duct, and jaundice is present, the death rate approaches 10 per cent, and the fatal cases are those in which operation has been delayed for diagnostic or other purpose Furthermore, there is no doubt that the majority of cases of carcinoma in or about the head of the pancreas reach the surgeon too late to permit of radical surgery

Since the diagnostic criteria can seldom be absolute, it is important to determine the relative emphasis to be placed on the several sources of evidence from which we try to reach our decision These sources are clinical and laboratory , but, of the two, the clinical observations are probably the more important It is manifestly impossible to discuss in any detail the clinical features of the many diseases which may give rise to jaundice , and I am content to make such points as have emerged from a review of my own cases, a series which is obviously not a comprehensive one, since it represents only the personal experience of a single individual

CLINICAL ASPECTS

The series consists of 93 patients, in 91 of whom a definite diagnosis was arrived at as follows —

Simple Causes—59 Cases	
Stone in common bile duct	40 cases
Subacute and chronic pancreatitis	6 ,,
Hepatitis and cirrhosis	6 ,,
Stricture of the common bile duct	3 ,,
Cystic disease of the head of the pancreas	2 ,,
Post-bulbar duodenal ulcer	1 ,,
Post-gastrectomy	1 case
Malignant Causes—32 Cases	
Carcinoma of pancreas and ampulla	21 cases
Carcinoma of gallbladder	5 ,,
Carcinoma of bile ducts	4 ,,
Primary carcinoma of liver	1 case
Secondary carcinoma of liver	1 ,,

Of the thirty-two patients with malignant jaundice, only two were under 50 years of age—a youth of 20 years with carcinoma of the hepatic duct, and a man aged 43 with secondary malignant disease of the liver originating in a carcinoma of the stomach In the simple group, fifteen patients were under 50, but only two of them had non-surgical lesions—in both cases post-hepatic fibrosis , and only two patients in the whole series were below the age of 40

Though patently a selected group of jaundiced patients in a single surgical charge, the figures have a certain significance , for the unit concerned is the only surgical service in the hospital, and may, therefore, be expected to deal with all jaundiced patients in which surgery is indicated Consequently, the infrequency of jaundice under the age of 40 in the series may be taken to imply that the obstructive type of regurgitation jaundice is rarely encountered under this age As a corollary, it is probably true to say that, below the age of 40, hepatitis is virtually the only cause of jaundice, but thereafter, regurgitation jaundice due to extrahepatic obstruction becomes increasingly common, though subacute hepatitis or cirrhosis account for a proportion of cases

A survey of the clinical findings and of the pre-operative diagnoses in this series has been both salutory and humiliating , and perhaps it is fortunate that time forbids a frank declaration of our diagnostic failures The conclusion—or the moral, if you will—is simply this that while the clinical features are sometimes decisive, and usually helpful, they can prove completely misleading

A scrutiny of the patients' history before the onset of jaundice illustrates this admirably , for although a succession of attacks of colicky pain in the upper abdomen, radiating to the back, and associated with tenderness in the right hypochondrium, usually indicates a gallstone obstruction, in two of our patients, the lesion discovered at operation was a subacute pancreatitis, and in another, a " typical " gallstone history led to operation during an attack of presumably unrelated infective hepatitis

A complaint of previous flatulent dyspepsia is notoriously unreliable in that it may point to disease of the biliary passages, but equally well to cirrhosis of the liver, though in the latter event, ascites, the occurrence of spider nævi, or the stigmata of portal hypertension may aid in its recognition

Loss of appetite and loss of weight are common both to chronic hepatitis and to malignant disease of the bile passages and the pancreas , and contrary to well-established belief, we have become increasingly aware that carcinoma of the pancreas is often a painful disease Indeed, pain is frequently the first evidence, preceding the onset of jaundice by several months and as it is sometimes periodic, it may bear a superficial resemblance to biliary colic, though more commonly, it assumes the character of a constant dull ache in the epigastrium and in the back

By contrast, the hepato-toxic jaundices are less frequently associated with frank pain The icterus may appear insiduously without initial symptom but there is often a prodromal period of vague ill health , and in rather more than half, there is an appreciable discomfort in the region of the liver which in those of low pain threshold is readily translated to pain

A strictly painless jaundice, indeed, is very rare , on the few occasions it has been encountered in this series it has been due mostly to cirrhosis, or to carcinoma of the bile ducts, or of the Vaterine ampulla , but every now and then a calculous obstruction of the common duct is quite painless, and the discovery of a stone affords the surgeon a pleasant surprise if a pre-operative diagnosis of malignant disease has been entertained

If the presence or absence of pain has to be treated with caution, so also must fluctuations in the depth of the jaundice Variation certainly implies a periodical diminution in the degree of regurgitation and, as such, is more likely to be encountered in extrahepatic obstruction due to a movable stone in the common bile duct By contrast, the jaundice resulting from a permanent and irremovable malignant obstruction is unremitting and steadily progressive, at least until a balance is struck between production and excretion It must be borne in mind, however, that all unremitting obstructions are not necessarily due to malignant disease of the extrahepatic ducts, for intrahepatic obliteration of the bile ducts in the healing stage of hepatitis may give rise to an icterus which is equally obstinate, and so may a stone which becomes firmly and permanently impacted in the duodenal papilla

In the acute and subacute stages of infective hepatitis the tendency is for the jaundice to disappear gradually, if somewhat slowly, after it has reached its peak This is also the usual course of the jaundice of calculous disease, though here the resolution is perhaps more rapid

The occurrence of hepatic fever, with rigors and general systemic upset, though it favours the diagnosis, is certainly not pathonomonic of stone in the common bile duct, ulceration of an ampullary growth, and subsequent infection, may also lead to cholangitis and to febrile attacks

The ulceration of a growth into the duodenum provides a diagnostic test of great importance, however, for the ulceration is usually attended by some degree of hæmorrhage, and a positive benzidine test for occult blood in the stool may be very helpful And yet that too can be misleading, for a patient recently investigated, with painless jaundice and a positive benzidine test, suspected of harbouring an ampullary cancer, proved at laparotomy to have a post-bulbar duodenal ulcer—the only example of this rare cause of jaundice I have encountered

Clinical examination may or may not be helpful Enlargement of the liver is common to hepatitis and to all the gradual obstructive lesions, nodularity both to cirrhosis and to carcinoma, and tenderness to hepatitis and to the obstructed liver of calculous disease, especially when infection is present Palpable distension of the gallbladder is a reliable sign of common duct obstruction, but in many cases the distended gallbladder is impalpable, and failure to define it in suspected carcinoma of the pancreas proves nothing The discovery of a palpable tumour in the vicinity of the pancreas is valuable, and so too are spider nævi, the presence of ascites, enlargement of the spleen, or the evidences of the establishment of a portal collateral circulation in the abdominal wall

Radiological examination is singularly unhelpful in the doubtful case Rarely a widening of the duodenal loop will indicate an enlargement of the pancreatic head, presumably due to tumour, and then advanced, and the demonstration of stones in the gallbladder may point to the probability of a calculous obstruction of the common duct, though now and then a double lesion—gallstones and carcinoma of the pancreas—is encountered, and negative radiological reports are valueless

It is obvious that in the absence of absolute values, a tentative clinical diagnosis can emerge only from an assessment of the balance of probabilities in each individual patient It may be taken a stage further—or even to certainty—by the employment of sundry laboratory tests

THE LABORATORY TESTS

The laboratory tests are principally concerned with the assessment of liver function, and with many facets of this difficult problem I am not qualified to deal A consideration that demands emphasis in relation to the laboratory tests in general, however, is that jaundice is a process, and not a state , and repeated laboratory tests will give a clearer picture of the process than single random observations

Thus a single examination of the urine and of the fæces, and estimation of the amount of bilirubin in the serum, will provide ready enough evidence that bile is being regurgitated after its manufacture by the liver cells, and that some only, or none, is reaching the intestine But daily determination of the stool content—by one of the quantative methods of urobilin estimation—will soon indicate if the process is an intermittent or a permanent one , and by and large, the total absence of bile on successive tests over five or six days is strongly suggestive of malignant obstruction of the bile ducts

Of the other tests, the estimation of the serum alkaline phosphate, the plasma proteins, and the cephalin-cholesterol flocculation test have proved most helpful in the present series Their principal value is early in the illness, for then in hepatitis the results may show a debasement of liver function which is almost invariably absent in duct obstruction, unless the jaundice is of long duration or complicated by infection

Alkaline phosphatase levels under thirty units (King-Bodansky) per 100 c c of serum with a positive flocculation test suggest hepatitis , whereas, most cases of complete duct obstruction have a phosphatase level above thirty-five units

In the interpretation of the flocculation tests, it must be borne in mind that in the presence of a total biliary obstruction too recently established to have induced liver damage, the flocculation tests may be positive because of unassociated disease, as, for example, cardiovascular disease , and, furthermore, uncomplicated and severe duct obstruction in an otherwise healthy person may never give rise to positive flocculation tests, even though liver biopsies at the time of operation show a marked degree of biliary cirrhosis The reason for this is not understood, but it is parallelled by the clinical well-being of many patients with intractable and long-standing obstructive jaundice

One additional test has proved of value in a double sense—the estimation of the prothrombin concentration In the first place a low concentration indicates the possibility of operation and post-operative hæmorrhage, and underlines the need for the vigorous prophylactic administration of vitamin K Furthermore, in obstructive jaundice where the prothrombin deficiency is due to lack of absorption of vitamin K from the intestine, rather than to inability of the liver cells to employ it in the manufacture of prothrombin, a rapid rise in concentration may follow, within a matter of hours, the intravenous administration of the vitamin This is in marked contrast to the poor or slow response elicited in hepatitis, where the low concentration of prothrombin is due to disablement of the liver cells

LIVER BIOPSY

A discussion on the diagnosis of jaundice would be incomplete without some reference to the place of liver biopsy in the diagnostic scheme The introduction of the needle-aspiration method has placed a new weapon in the hands of the clinician, but its value in diagnosis is hard to assess The tissue removed is too scanty to make for easy histological study, and biliary cirrhosis secondary to obstruction appears difficult to distinguish from the ordinary portal cirrhosis A disturbing feature of our obstruction cases has been the absence of appreciable dilatation of the smaller bile ducts in the portal tracts, which would have provided unequivocal evidence of biliary obstruction The risks of needle biopsy are perhaps slight, and it may be valuable in following the course of an infective jaundice, but in the elucidation of the diagnosis, it has proved of little or no value in the present series

In summary, then, it is probably true that a reasonably accurate diagnosis of obstructive jaundice can be made from a survey of the history, the clinical features, and the results of certain laboratory tests Indeed, it is often possible to indicate the probable nature of the obstruction, though this is of less importance, and delay in attempting such precision is unjustifiable, since timely surgery has so much to offer the patient with obstructive jaundice, either in the shape of radical or effectively palliative procedures

In a minority of patients the resources at our disposal will be inadequate to ensure a confident diagnosis, and an extrahepatic, and therefore a potentially remediable obstruction cannot either be disproved, or established beyond doubt It is this occasional circumstance that is so fraught with danger, delay may render a duct carcinoma or a pancreatic tumour inoperable, or at least irremovable, and even when the obstructing agent is simple, it may prejudice the issue by the effect of the long obstruction or of infection on the health of the liver cells If the exact cause of a regurgitation jaundice has not been determined in 10 to 14 days, therefore, the patient should certainly be submitted to operation The argument that it is dangerous to operate on a patient with hepatitis or severe liver disease is less valid in these days of improved anæsthesia, and better control of the fluid and other metabolic needs of the patient It is now better, in fact, to look and see than to wait and see

BIOCHEMICAL TESTS IN THE DIAGNOSIS OF JAUNDICE

A Preliminary Analysis of 107 Cases

By J D S CAMERON, C B E, T D, M D, F R C P Ed, and
R F ROBERTSON, M B, F R C P Ed, M R C P

PROFESSOR ILLINGWORTH and Mr Bruce have presented their experiences in the diagnosis of jaundice from the surgical point of view The purpose of this paper is to present a short survey of jaundice from the medical point of view The survey is based on a series of 107 cases of jaundice comprising consecutive admissions to two medical charges in the Royal Infirmary of Edinburgh over a period of 2½ years and cases seen by one of us in private consulting practice over the same period

Table I shows the distribution of ultimate diagnosis in the 107 cases Few comments on this table are required In its broad outline, it is seen that 49 cases can be classified as "medical" jaundice and 58 cases as "surgical" jaundice For convenience, homologous serum jaundice, of which there was only one case, is included as infective hepatitis Of the 8 cases of diffuse hepatic fibrosis few occurred in chronic alcoholics, most having no obvious ætiological factors The surgical cases are self-explanatory, except perhaps the two cases of duodenal ulcer In those two cases, exploratory laparotomy revealed

TABLE I

Diagnosis in 107 Cases of Jaundice

Acute Parenchymatous Hepatic Disease—			
Infective hepatitis		34	
Acute hepatic necrosis		3	
Weil's disease		3	
		—	40
Chronic Parenchymatous Hepatic Disease—			
Diffuse hepatic fibrosis		8	
Hæmochromatosis		1	
		—	9
Obstructive Lesions in Biliary Passages—			
Cholelithiasis		21	
Duodenal ulcer		2	
Primary tumours—			
Carcinoma of pancreas	9		
(?) Carcinoma of pancreas	2		
Carcinoma of bile ducts	4		
Carcinoma of duodenum	1		
Carcinoma of gallbladder	1		
Simple tumour of pancreas	1		
Primary carcinoma of liver	1		
	—	19	
Secondary tumours in liver		15	
Unspecified tumour		1	
		—	58

Read at a joint meeting of the Medico Chirurgical Societies of Edinburgh and Glasgow in Edinburgh on 23rd November 1951 they become less anomalous on repetition of the tests at weekly intervals Sometimes biochemical tests other than those mentioned may help, *e g* other flocculation tests such as the thymol turbidity or thymol flocculation One should not advise early laparotomy in this type of case when the age is under 40 , a further period of observation may —and usually does—provide confirmatory evidence that the jaundice is medical In the weeks of waiting the tests should be repeated , they may at any time solve the problem In the end, if no solution is obvious after four to six weks of observation and the jaundice is not lessening, laparotomy should be performed

TABLE VIII

Jaundiced Patients under 40 *Years of Age*
Suggested Scheme of Management

(Jaundice present approximately 2 weeks)

Cephalin Cholesterol	Alkaline Phosphatase	
(1) +3 +4	3 29	Medical treatment
Neg (2) +1 +2	30+	Immediate laparotomy
(3) Anomalous		i Period of observation ii Repeat biochemistry iii Delayed laparatomy

In patients over 40 years of age, the policy just described would be disastrous because of the greater possibility of obstructive jaundice often due to neoplasm The patient should not remain uninvestigated for two weeks , biochemical tests should be arranged immediately jaundice becomes apparent, and the scheme of management indicated in Table IX adopted

TABLE IX

Jaundiced Patients over 40 *Years of Age*
Suggested Scheme of Management

(Jaundice present only a few days)

Cephalin Cholesterol	Alkaline Phosphatase	
(1) +3 +4	3 29	Medical treatment
Neg (2) +1 +2	30+	Immediate laparotomy
(3) Anomalous		i Maximum period of observation one week ii No delay in laparotomy

Combination (1) and combination (2) are the same as in the under 40 table, apart from their relative frequency Combination (2) is now the more common , combination (1) as indicated earlier in the age incidence of infective hepatitis, is not so uncommon as is generally thought In the anomalous combinations, one should not study the patient for weeks, as in the under 40 group A single repetition of biochemical tests may be arranged and may solve the problem Time should not be wasted on radiology The risk of neoplasm is so great that laparotomy should be done early rather than late

In conclusion it is emphasised that the schemes presented are by no means infallible and will occasionally mean needless laparotomy in a case of infective hepatitis In our present state of knowledge this is inevitable, but is justified by the high incidence of carcinoma as a cause of biliary obstruction

We wish to thank Dr W D D Small and Dr W A Alexander for permission to study cases admitted to their charge in the Royal Infirmary of Edinburgh

Discussion

Mr W A Mackey, opening the discussion, was of the opinion that everyone endorsed Professor Illingworth's plea for diagnostic laparotomy in cases of doubt

He wished to offer a few brief comments on the diagnosis of carcinoma of the pancreas One was the period of months of mysterious recurring malaise preceding the onset of jaundice

He had seen a case recently where, after a period of some weeks of observation and investigation, a diagnosis of steatorrhœa had been adopted until jaundice appeared, when carcinoma of the pancreas was diagnosed

Another case was that of an elderly lady with intense skin itching of many months' duration It was, at first, thought to be "senile pruritus" until jaundice appeared, when carcinoma was diagnosed

Mr T McW Millar said that during the last few years he had been interested in this subject from the surgical point of view Professor Illingworth had shown clearly that the most difficult age period was between 40 and 60—before 40 the vast majority of cases were medical, after 60, surgical All speakers had referred to the rarity of a surgical condition under 40 Mr Millar thought it wise to remember that carcinoma does occur under that age In a patient in this age period whose jaundice was not clearing up, there should be a review of the diagnosis, and laparotomy should be considered

The importance of a clinical history had been emphasised but Mr Millar doubted whether the history given was always reliable He quoted one case of prolonged jaundice in which a confident diagnosis of carcinoma had been made, but on going personally into the history and eliciting a story of a single attack of pain a year previously which was almost certainly a biliary colic, he diagnosed calculous obstruction which was confirmed at operation

Mr Millar agreed with Mr Bruce that an ampullary carcinoma was more hopeful from the surgical point of view A benzidine test was almost always positive in papillo-ampullary lesions and was a useful diagnostic procedure

Mr Millar emphasised the need for surgical exploration without delay in doubtful cases

Dr Batty agreed that laparotomy was very frequently essential He drew attention to the difficulties which the surgeon might encounter in arriving at correct diagnosis by mentioning recent experience in two cases of obstructive jaundice in middle-aged women One of these patients subjected to laparotomy had the abdomen closed as the surgeon was unable to detect pathology Subsequent operation, three months later, showed extensive carcinoma of the biliary tract In the other case, diagnostic laparotomy revealed a hard nodule in relation to the lower end of the bile duct Extensive resection was performed with recovery of the patient Pathological examination of the excised tissue failed to reveal malignant disease The nodule was made up of fibrous tissue only

Professor Illingworth, replying, said that it was remarkable that carcinoma of the head of the pancreas so rarely gave rise to gross steatorrhœa though minor changes in the fæcal fat content were not unusual Perhaps the explanation was that when the main pancreatic duct was blocked by the growth, pancreatic secretion sometimes escaped by communicating channels into the duct of Santorini

He agreed with Mr Millar that occult blood might be found in the stools, especially if the growth was ulcerating into the duodenum, but he believed that a negative finding carried no significance

Dr J D S Cameron, replying on behalf of Dr Robertson and himself, remarked on the harmony which characterised the Joint Meetings with the Glasgow Society The present meeting was remarkable for the harmony of views, surgical and medical, expressed in the three papers, a harmony so complete that it required to be stated that there was no collaboration between the speakers, each arrived at the opinions expressed in complete independence

He agreed that in patients over 40 surgery should always be considered, after 40 a patient had nothing to lose and everything to gain by early exploratory operation

Some of the points raised called for a little amplification All had agreed that the interpretation of liver function tests required not only knowledge but judgment Dr Cameron suggested that the scheme put forward by Dr Robertson and himself be accepted as a working basis If interpreted with judgment, the scheme indicated quickly, in many cases, the correct course of procedure

Mr Bruce had emphasised that clinical knowledge formed the basis of diagnosis Dr Cameron said that they were not attempting to suggest that laboratory tests came before clinical diagnosis, rather that they were ancillary to it Tests should be applied quickly, and repeated immediately if necessary to allow of the earliest possible distinction of medical and surgical jaundice Dr Cameron said that in an anomolous case minor cephalin cholesterol flocculation gave a weighting towards surgery, whereas major flocculation gave a weighting towards medical treatment The cephalin cholesterol flocculation test should if possible never be allowed to stand alone in a doubtful diagnosis Laboratory tests were often at variance with each other—it was sometimes necessary to do tests other than the cephalin cholesterol flocculation, *e g* thymol flocculation, to demonstrate parenchymal damage

Dr Cameron considered X-rays to be a waste of time in cases where early operation was indicated—one had to wait for an appointment and then the result was often unhelpful Where there was no urgency radiology was employed as ancillary

Professor Illingworth had said that deep jaundice was no longer a danger in surgery The jaundice never had been, parenchymal damage had always been the danger and the assessment of the degree of this functional damage was a further indication for the employment of the biochemical tests The degree of parenchymal damage did not run parallel with the depth of the jaundice

INDEX

Transactions of the Medico Chirurgical Society of Edinburgh

ADAMSON, W A D , Hæmatemesis and melæna, 41
Addison's disease, The diagnosis of, by T W G Kinnear, 63
—— —— The treatment of, by C F Rolland, 70
—— —— Prognosis in, by J D Matthews, 76
Anderson, Thomas, A review of infectious diseases during the first half of this century Changing concepts in the common fevers, 22

Batty, D M F , Hæmatemesis and melæna, 33
Brown, J J Mason, Surgical aspects of vomiting in the newborn, 51
Bruce, John, The diagnosis of jaundice, 88

Cameron, J D S , and Robertson, R F , Biochemical tests in the diagnosis of jaundice, 95
Cardiospasm, Dysphagia with special reference to, by J M Graham, 1

Dysphagia with special reference to cardiospasm, by J M Graham, 1

Graham, James M , Dysphagia with special reference to cardiospasm, 1

Hæmatemesis and melæna, by D M F Batty, 33 , by W A D Adamson, 41

Illingworth, C F W , The diagnosis of jaundice, 83
Infectious diseases, A review of, during the first half of this century Changing concepts in the common fevers, by Thomas Anderson, 22
—— A review of, during the first half of this century The incidence of infectious diseases, 1900 1950, by Alexander Joe, 15

Jaundice, The diagnosis of, by C F W Illingworth, 83
—— —— by John Bruce, 88
—— —— Biochemical tests in, by J D S Cameron and R F Robertson, 95
Joe, Alexander, A review of infectious diseases during the first half of this century The incidence of infectious diseases, 1900 1950, 15

Kinnear, T W G , The diagnosis of Addison's disease, 63

Matthews, J D , Prognosis in Addison's disease, 76
Melæna, Hæmatemesis and, by D M F Batty, 33 , by W A D Adamson, 41

Newborn, Surgical aspects of vomiting in the, by J J Mason Brown, 51

Office Bearers, Election of, opposite p 1

Robertson, R F , *see* Cameron J D S and Robertson, R F , 95
Rolland, C F , The treatment of Addison's disease, 70

Vomiting, Surgical aspects of, in the newborn, by J J Mason Brown, 51

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The Transactions
of the
Edinburgh Obstetrical Society

SESSION CIV—1951-1952

AT a Meeting of the Edinburgh Obstetrical Society, held on 14th November 1951, with the President, Dr E Chalmers Fahmy, in the Chair, the following were elected Office-Bearers for Session 1951-52.

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The Transactions
# of the
Edinburgh Obstetrical Society

THE SHAPE AND SIZE OF THE FEMALE PELVIS

By ROBERT M BERNARD, M R C O G
Department of Midwifery, University of Aberdeen

IMPROVEMENTS in the technique of pelvic radiography in recent years have led to a renewed interest in the variations in shape and size of the female pelvis Caldwell and Moloy[1] and their co-workers suggested that the shape of the pelvis is determined chiefly by evolutionary and hormonal influences Others, notably Thoms[2] in America, Nicholson[3] in England, and Allen[4] in New Zealand, believe that nutrition is the most important factor The results of investigations in the Aberdeen Maternity Hospital show that the shape and size of the pelvic brim are closely connected with stature, and suggest that environment through its influence on stature, is probably the greatest single factor influencing the development and the ultimate shape and size of the pelvis During childhood and adolescence a good environment encourages optimal growth, and as a result, the pelvic brim reaches its full size and is round or long oval in shape On the other hand, a poor environment with all it implies—poor diet, poor housing conditions with overcrowding, lack of fresh air and sunshine, and lack of exercise—stunts the growth and as a result the pelvic brim is not only smaller than it should be but is flattened, particularly in the posterior segment

It has also been found that the shape of the pelvic brim is not basically different in the male and female, and that similar deformities may result from the same influences in either sex

The preliminary investigation discussed in this paper is concerned only with the pelvic brim

FEMALES

Investigation —It is no new concept that the shape of the pelvis is related to general physique Thoms compared student nurses with clinic patients and found that women with long oval pelves were predominantly tall, broad shouldered and narrow hipped, whilst those with transversely oval pelves were shorter with broad hips in proportion to the shoulders , the women with round pelves were of intermediate build

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Paper read to the Edinburgh Obstetrical Society on Wednesday, 14th March 1951

It was noted in Aberdeen that tall women seldom had difficulty in labour due to mechanical causes, whereas obstructed labour was relatively common amongst small women The degree of difficulty seemed to be inversely proportional to height, and serious disproportion at the brim was rare in women over 5 ft 2 ins tall

It was decided, therefore, to study two groups of patients, 100 *over 5 ft 5 ins and 100 under 5 ft in height All the patients were* under 30 years of age and booked for confinement in the Aberdeen Maternity Hospital All were studied either during their first pregnancy or so soon afterwards that accurate information about the labour was available

TABLE I

Pelvic Type Incidence in Females by Height

Pelvic Type	Tall (100)	Small (100)
Round	87	65
Narrow	6	Nil
Flat	7	34
Scutiform	Nil	1

A thorough physical examination and complete X-ray pelvimetry was carried out in each case The following radiographs were taken —

(*a*) An erect lateral radiograph using the technique described by Moir [5]

(*b*) An outlet radiograph by the Chassard-Lapine [6] technique.

(*c*) Stereo films of the brim with its plane horizontal, together with one centred film

Pelvic Brim Classification —Four basic shapes of the pelvic brim are generally described—round, long oval, flat and triangular, referred to by Caldwell and Moloy as gynæcoid, anthropoid, flat and android One disadvantage of this classification is that, since it is based on visual impressions of shape, it is to some degree subjective and individual variations make accurate comparison difficult For this reason the classification suggested by Nicholson, which is based solely on measurement, was used in this study Fig 1 shows the different pelvic brim shapes classified according to Nicholson, and to Caldwell and Moloy

Incidence of Pelvic Types —Table I shows the incidence of the different pelvic types in the two groups of women, tall and small Whilst there are fewer round pelves amongst the small women, the most significant feature is that there are considerably more flat pelves, 34 as against 7 It can be calculated from Thoms' figures that in his series the average height of the nurses was 5 ft 5 ins and that of the clinic patients 5 ft 2 ins , a round or anthropoid pelvic brim was found in 80 per cent of the nurses and in only 60 per cent, of the clinic patients. findings which are very similar to those in Table I In the present series only one brim of the whole 200 could be described as scutiform, *i e* with the very flat posterior segment said to be so characteristic of the " male " or " android " pelvis

Influence of Environment—The incidence of flat pelves among small women in this series, approximately one in every three, has been confirmed by further routing X-ray examination of all women under 5 ft 1 in in height attending the clinic The same proportion was found in the next 200 cases examined If this pelvic shape is a " normal " growth variant as Caldwell and Moloy suggested, it should surely be found as often among tall as among small women Since, in fact, a flat pelvis occurs much more frequently among small women, some common factor must be found to account for both pelvic flattening and short stature and this factor is most likely to be environmental

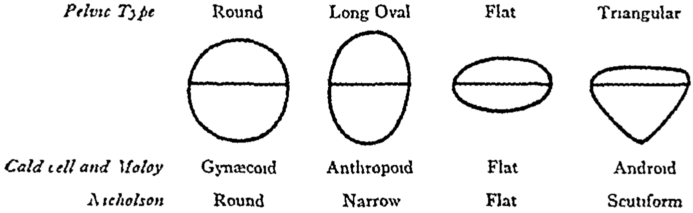


FIG 1 —Pelvic brim classification

Nicholson classified the pelvic brim as follows —

Flat	Brim index 81 per cent or less
Narrow	Brim index 104 per cent or less
Scutiform	Sagittal index 30 per cent or less with brim index of between 81 and 104 per cent
Round	All the remainder

It should be noted that the use of such limited measurements will not clearly indicate the precise shape of the pelvic brim Nevertheless in practice the " android " shape and certainly the shape of the " android " posterior segment, for example, can, as a general rule, be inferred from the use of the term " scutiform "

Even although her parents may also be small, there is no proof that the stature of a small woman is inherited Heredity only determines the potentials of an individual, whereas environment determines how far these potentials are achieved It is probable that in some families at least the same type of unfavourable environment has prevented full growth in both parents and offspring

There is sufficient evidence in the literature to show that environmental factors, of which nutrition must obviously be one of the most important, can have a marked effect on height and state of health As an example, Shapiro [7] showed that the offspring of Japanese immigrants to Hawaii, with an improved standard of living, were much taller than their blood relatives bred in Japan

Only a few clinical surveys have been made of families at different income levels, but these show differences in physique and stature which could have been anticipated In 1945, Baird,[8] surveying groups of private and hospital class patients, found that only 5 per cent of the private patients were under 5 ft 1 in in height, while by contrast

26 per cent of the hospital class came into this category Most of the private patients belonged to the Registrar-General's Social Classes I and II, and the hospital patients to Social Classes III, IV and V The Registrar-General's classification is based on the occupation of the husband Social Class I includes the professional classes, Social Class III the skilled workers, and Social Class V the unskilled workers ; Classes II and IV are intermediate Although the classification is somewhat arbitrary it has proved highly valid and gives a useful index of the variation in living standards within a community In Baird's series, the private patients were considered to be of better physique than the hospital patients, and within the latter group a detailed physical examination showed that taller women as a group were healthier than the small

If environment were to be assessed accurately, a prolonged study over many years of individuals, their diets, housing conditions and all the other factors which serve to make up environment, would be necessary Failing this a useful assessment should be obtained by

(1) noting the place of upbringing, the father's occupation and social class, and the number of other children in the parents' household

(2) studying the end result of environmental influences, *e g* the present physical state of the individual, which is unlikely to vary very much, since most people tend to live their adult life under conditions analogous to those of their upbringing

TABLE II

Size of Family of Upbringing by Social Class of Father

		Social Class		Unclassifiable
		I and II	III IV and V	
Small women	Number of cases	4	90	6
	Size of family	2 5	5 5	
Tall women	Number of cases	18	74	8
	Size of family	2 9	3 6	

In this series, as had been expected, more of the small women had grown up in poorer parts of the city and in larger families than had the tall women In Table II the Social Class of the patient's father and the average size of the family of upbringing are compared Only 4 of the small women came from Social Classes I and II The average number of children in the family of upbringing was 2 5 The rest came from Social Classes III, IV and V, with a size of family averaging 5 5. Eighteen of the tall women were from Social Classes I and II, and the average number of children in their families was 2 9 The remainder from Social Classes III, IV and V came from families averaging 3 6 While social data was not obtainable from all patients these figures leave no doubt that more tall women than small women came from the higher social classes and from considerably smaller families In the lower income groups the larger the family the worse the environment, and the majority of the small women had grown up in such circumstances

As already stated each woman was examined clinically before being X-rayed , she was placed in one of two grades according to whether her state of physical well-being was judged to be superior or inferior In general terms a patient of superior physique (Grade I) has a healthy appearance and good colour, is well proportioned and is neither under nor over-weight , her skin has a healthy bloom, and her teeth, gums, hair and nails are in good condition A woman failing to meet these standards is classed as of inferior physique (Grade II)

In this series only 19 of the 100 small women were graded superior as opposed to 76 of the 100 tall women

It has been suggested that preconceived ideas may have resulted in a tendency to grade tall women as good and small women as poor

TABLE III

Pelvic Type Incidence by Physique

	Tall Women			Small Women	
	Grade I	Grade II		Grade I	Grade II
Round	88 2%	83 3%	Normal pelvic shapes	73 6%	63 0%
Narrow	6 6%	4 2%		0 0%	0 0%
Flat	5 2%	12 5%	Abnormal pelvic shapes	26 4%	35 8%
Scutiform	0 0%	0 0%		0 0%	1 2%
Number of cases	76 (100%)	24 (100%)		19 (100%)	81 (100%)

From the outset I was thoroughly alive to this possibility, and strove to assess each patient on her general physique without respect to height The following correlation between this rather rough physical grading and pelvic form would appear to show that the effort must have been for the most part successful

Physique and Pelvic Shape—Table III shows the relationship between physical grade, height and pelvic shape In both tall and small groups those women graded as physically inferior show an increased incidence of the abnormal pelvic shapes, the flat and scutiform and proportionally less round or narrow Of course some abnormal pelves were also found amongst the women graded as physically superior, but a comparison of the degree of flattening in these pelves as gauged by the brim index showed that pelvic flattening is much less marked amongst these women of better physique

In order to measure varying degrees of difference in the shape of the pelvic brim three main indices were adopted as follows —

$$(1)\ \text{The brim index} = \frac{\text{antero-posterior diameter}}{\text{widest transverse diameter}} \times 100 \text{ per cent },$$

this provides a broad indication of the curvature of the brim as a whole.

(2) The sagittal index

$$= \frac{\text{antero-posterior diameter of posterior segment}}{\text{antero-posterior diameter of brim}} \times 100 \text{ per cent}$$

A low index indicates that the posterior segment is relatively flat and in practice absolutely flat in most cases

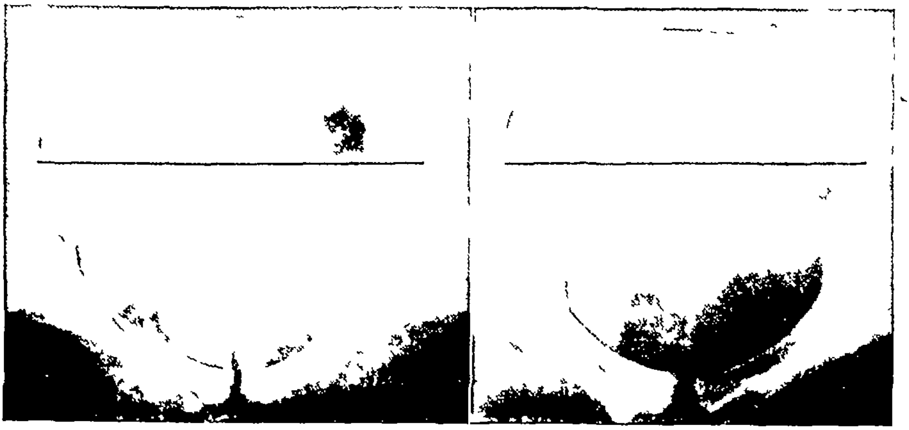
(3) An index I have called the posterior sagittal-transverse index This expresses the ratio of the posterior sagittal diameter to the widest transverse diameter as a percentage As this index relates the depth of the posterior segment to its width, it provides a more accurate assessment of the curvature of the posterior brim segment than does the sagittal index and is thus a more sensitive means of measuring flattening of that segment

TABLE IV

Indices of Curvature by Height

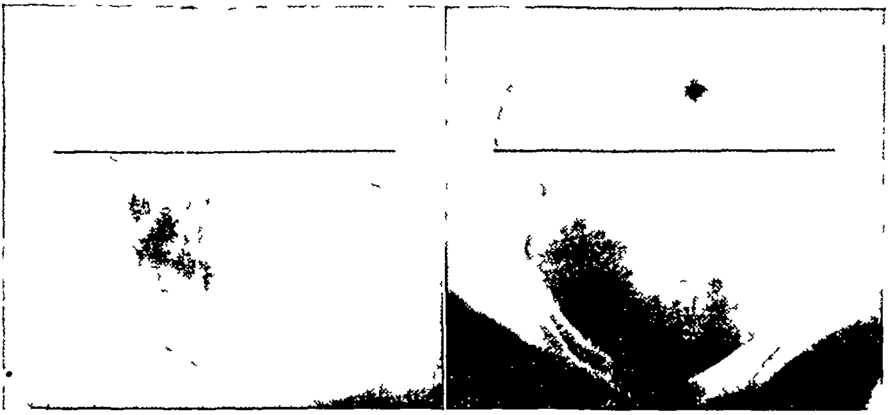
		Tall Women	Small Women	All Heights	Difference
Brim index (percentage)	Grade I	92 48	86 35	89 42	2 75±1 48
	Grade II	88 60	84 74	86 67	
	All grades	91 61	85 05		
	Difference	6 56±1 19			
Sagittal index (percentage)	Grade I	39 38	40 34	39 86	1 86±0 64
	Grade II	38 45	37 54	38 00	
	All grades	39 17	38 08		
	Difference	1 09±0 52			
Posterior sagittal transverse index (percentage)	Grade I	36 49	34 95	35 72	2 78±0 88
	Grade II	34 06	31 82	32 94	
	All grades	35 95	32 42		
	Difference	3 53±0 71			

Table IV shows the mean values of each of these indices in the two groups of women classified by physique Each index is less in the



FIGS 2*a* and 2*b*

	2*a* (Mrs S)	2*b* (Mr I)
Height	5 ft 6½ ins	5 ft 9 ins
Physical grade	I	I
Pelvic brim index	93 4 per cent	98 5 per cent
Sagittal index	41 6 per cent	42 7 per cent
True conjugate diameter	12 1 cm	12 9 cm



FIGS 3*a* and 3*b*

	3*a* (Mrs F)	3*b* (Mr M)
Height	5 ft 5½ ins	6 ft 2½ ins
Physical grade	I	I
Pelvic brim index	106 7 per cent	100 0 per cent
Sagittal index	43 0 per cent	39 0 per cent
True conjugate diameter	12 7 cm	13 0 cm

women of poor physique than in those of good physique and this means that in both small and tall women, the pelvic brim as a whole and the posterior segment in particular is more flattened in the women of poorer development

Physique and Pelvic Size—Poor general growth affects not only the shape of the pelvic brim but also its size This is best shown by a consideration of two of the most practically useful indices of the actual capacity of the brim—the brim area and the true conjugate diameter

Table V compares the mean values of these two measurements in both height groups in relation to physical grade The trend is the same as in the previous table Not only is there a very marked difference in capacity between the " tall " and the " small " but inside each group the pelvic brims of women of good physique are more spacious than those of inferior physique

A knowledge of the brim area is a useful guide to the possible outcome of labour although its value is limited by other variables such as the size and position of the fœtal head and the strength of the forces It would appear from a study of the literature that the figure for a " normal " pelvis lies somewhere between 110 to 130 sq cm The mean value in the group of small women of poor physique is 106 sq cm while even in the small women of superior physique it is just on the borderline of normal with a mean value of 109 9 sq cm In point of fact 27 of these small women had a pelvic brim area of below 100 sq cm and 8 an area of below 90 sq cm Since difficulties in labour due to disproportion occur quite often when the area is below 100 sq cm , if the infant is of average size or more, many of these small women would be candidates for difficult labour, but fortunately many of them produce small babies

TABLE V

Pelvic Brim Capacity by Height

		100 Tall Women	100 Small Women	All Heights	Difference
Brim area (sq cms) (Nicholson's formula $d'/2\ d''/2$)	Grade I	138 5	109 9	123 7	3 6 ±2 0
	Grade II	134 2	106 0	120 1	
	All grades	137 6	106 8		
	Difference	30 8±1 6			
True conjugate diameter (cms)	Grade I	12 80	11 01	11 90	0 38±0 15
	Grade II	12 33	10 71	11 52	
	All grades	12 69	10 77		
	Difference	1 92±0 12			

On the other hand, in the tall women the mean brim area of 137 6 sq cm is well above the " normal " range, in no case being less than 110 sq cm , while it was less than 120 sq cm in only 8 instances With such a brim capacity, even if the infant were large, there should be no mechanical difficulty at the brim unless the true conjugate diameter were small This was, however, not the case Only 6 out of the 100 tall women were found to have a true conjugate diameter of less than 11 4 cm ($4\frac{1}{2}$ ins), a measurement which is nowadays considered "normal" In all but one of the 6, the measurement was 11 1 cm (4 4 ins) and in the single case 10 5 cm (4 2 ins) a measurement which used to be considered by many as normal In the small women, the average measurement of 11 01 cm (or very nearly 4 4 ins) for the conjugate diameter in those women of good physique would seem reasonably satisfactory from the practical point of view In the small women of poor physique, however, the true conjugate diameter measured actually below 10 cm (3 9 ins) in 21 cases, and in each the pelvis was flat

It would therefore appear that small women have small pelves which are also often flat, and in the women of poor physique the number with flat pelves is much increased In tall women, the pelvic brim is large and well curved, but in those of inferior physique flattening also occurs, although to a much less marked degree than in small women It would seem as though there was a maximum "normal" height for human races and the nearer the actual height of an individual approaches this "ceiling" the less is there likely to be any defect of growth and thus of flattening of the pelvis

Hormonal Influences—It has been suggested by Caldwell and Moloy and others that flattening of the posterior segment, especially when associated with an angulated forepelvis, is due to the effect of a male hormone influence, hence the term android pelvis In a series of pelves they classified 2 6 per cent as flat and 32 5 per cent as android, and these were described as normal growth variants Since the android pelvis was found to be frequently associated with difficult labour, it would seem more probable that this pelvic shape is not a normal but literally an abnormal growth variant

In Aberdeen, during the last decade, it has been the routine practice to carry out X-ray pelvimetry whenever there has been any difficulty in labour In spite of this only a few examples have been seen of a pelvic brim which could be considered typically android in shape If, as has been suggested, this type of pelvis is associated with difficult labour in from 20 to 30 per cent of cases, then many more should have been seen Of course visual impressions do vary and it may be that a shape some call android we describe as flat, and *vice versa*—nevertheless, a really triangular shape is rarely seen in this clinic Caldwell and Moloy have included very few actual measurements in their publications Those published referred to the original series of dried museum specimens upon which their classification is based One of the most significant features of these is the low value given for the true conjugate diameter in the android pelvis, 10 7 cm (4 2 ins) and in the flat pelvis 8 4 cm (3 3 ins) It would seem probable that these museum specimens were almost certain to have been obtained from the poorer undernourished classes and if so these values are not surprising Certainly a measurement as low as 8 4 cm would only be seen in this country in women with definite clinical evidence of stunted growth

In view of difficulties in classification based on visual impressions of brim shape, Steele and Javert [9] tried to reduce the Caldwell and Moloy classification to terms of measurement by the use of special indices They based their suggested ranges of measurement for the different pelvic types on a series of 1000 radiographs It is rather significant that they also suggest a low measurement for the length of the conjugate diameter (obstetric) in both the " android " and the flat pelves—10 2 cm (4 ins) for a pure " android," 10 9 cm (4 3 ins) for a mixed " android " and 10 6 cm (4 2 ins) for the flat pelvis Using 10 5 cm as the dividing line between normal and contracted pelves they found that over 80 per cent of the " normal " pelves in their series were either gynæcoid or anthropoid in shape whilst nearly half the " contracted " pelves were either platypelloid or android In fact they concluded that size may be useful clinically as a fairly accurate means of predicting pelvic shape In the light of this evidence it is difficult to see how platypelloid and " android " pelves can be classed as " normal " growth variants Moreover, since the average male is taller than the average female, the effect of any postulated male hormonal influence might be expected to be found more often among tall women, but in fact such women as a group have large and well curved pelves

All evidence seems to point to the fact that any pelvis with a large true conjugate diameter is very seldom flat or " android " in shape It seems logical to believe that the " android " shape is only a modification of the flat shape and that both are due to the same cause, stunted growth

MALES

It had long been accepted that the male pelvic brim is typically " android " in shape until the work of Thoms [10] and of Ince and Young [11] cast considerable doubt on this belief In their series they found that the brim shape was most frequently round In the light of their work it was considered that the android shape was probably as abnormal in men as it is in women, brought about by the same influences, poor growth

A somewhat similar investigation was therefore carried out in males All male medical students attending the anatomy class of Aberdeen University were studied on the assumption that they would represent a group of healthy men, bred in a good environment Physical assessment and X-ray pelvimetry were carried out in the same manner as in the women

The following is a consideration of some of the results found in the first 100 students studied

The distribution of the various shapes of pelvic brim amongst these students is shown in Table VI The round pelvis was found in 80 per cent of cases and in fact only 3 scutiform pelves and 7 flat pelves were found, *i e* only 10 pelves showed flattening of any degree These findings are in very fair agreement with those of Thoms, who examined 69 students and came to the conclusion that the male pelvic brim showed the same variations as the female, each occurring with much the same frequency Figs 2*b* and 3*b* are radiographs showing the typical shapes of the pelvic brim found amongst the majority of these Aberdeen medical students These shapes closely resemble those seen amongst the tall females (Figs 2*a* and 3*a*)

The high proportion of round and narrow (or long oval) pelves amongst the students probably results from good environment during growth As one would expect, 70 per cent of these medical students came from families in Social Classes I and II The family of upbringing averaged only 2 9, even in the case of students from Classes III, IV and V As a group they were tall, the average height being 5 ft 9½ ins, and their physique was good Table VII shows that 79 per cent. were graded I There were only 6 under 5 ft 6 ins in height, but even these belonged to Grade I

TABLE VI

Pelvic Type Incidence in 100 *Male Students*

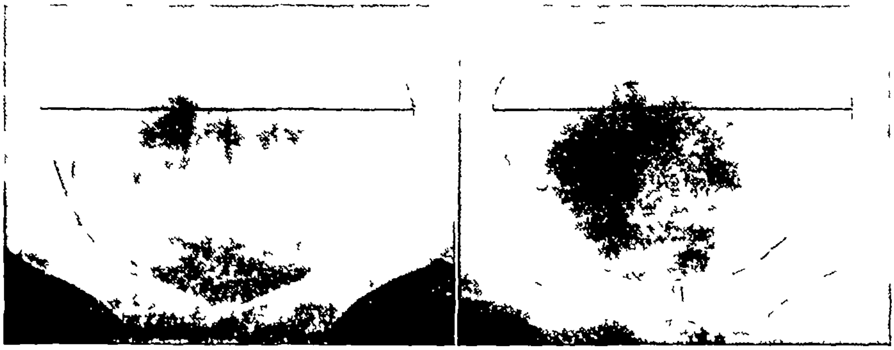
Pelvic Type	Number of Cases
Round	80
Narrow	10
Flat	7
Scutiform	3
Total	100

TABLE VII

Physical Grades in Relation to Height in 100 *Male Students*

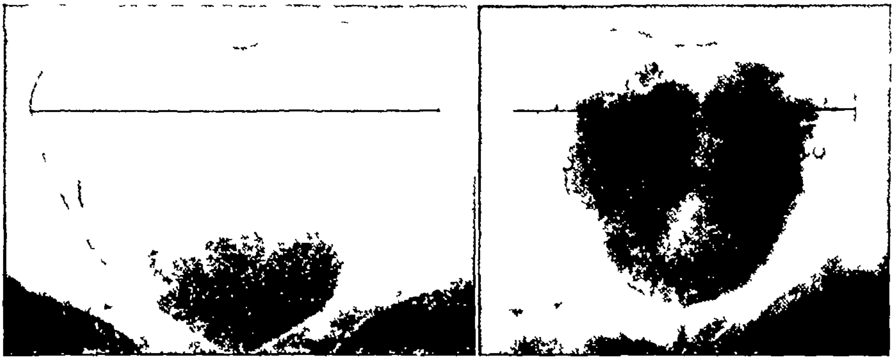
	Over 5 ft 10 ins	5 ft 6 ins 5 ft 10 ins	Under 5 ft 6 ins	All Heights
Grade I	36	37	6	79
Grade II	6	15	Nil	21
All grades	42	52	6	100

Since there were obviously few small men among the students, I looked amongst the less well-do-do classes for men under 5 ft 6 ins in height To date, 39 men in this category have been examined, recruited from varying sources—husbands of hospital patients, factory workers, and soldiers from the local barracks, all from Social Classes III, IV and V Most of these men were actually under 5 ft 2 ins



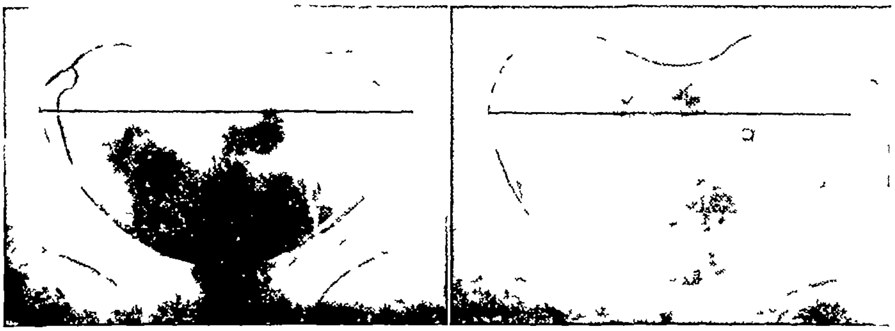
FIGS 4*a* and 4*b*

	4*a* (Mrs S)	4*b* (Mr F)
Height	4 ft 11 ins	5 ft 2 ins
Physical grade	II	II
Pelvic brim index	79 8 per cent	71 4 per cent
Sagittal index	32 0 per cent	29 5 per cent
True conjugate diameter	9 4 cm	9 0 cm



FIGS 5*a* and 5*b*

	5*a* (Mrs P)	5*b* (Mr B)
Height	4 ft 11½ ins	5 ft 1 in
Physical grade	II	II
Pelvic brim index	77 0 per cent	78 2 per cent
Sagittal index	22 4 per cent	25 5 per cent
True conjugate diameter	10 4 cm	9 0 cm



FIGS 6*a* and 6*b*

	6*a* (Mrs M)	6*b* (Mr M)
Height	4 ft 8½ ins	5 ft 0½ in
Physical grade	II	II
Pelvic brim index	65 8 per cent	58 6 per cent
Sagittal index	23 2 per cent	22 5 per cent
True conjugate diameter	7 5 cm	7 1 cm

In the vast majority of cases where flattening of the pelvis of a less marked degree (*vide* Figs 4 and 5) was present there was no evidence of rickets on clinical examination or in radiographs of the skull and long bones

in height, which for a man is very small indeed The average size of the family of upbringing was 5 5, the same as in the comparable group of small women

Table VIII shows the incidence of the pelvic types amongst these 39 men Forty-one per cent had a flat pelvic brim and 13 per cent a scutiform, *i e* 21 men or 54 per cent showed evidence of flattening of the pelvis, a far higher proportion than occurred among the students

Thirty-one out of the 39, or 80 per cent, were graded as of inferior physique (Grade II) Some of the poorest physical types were found among the soldiers These men had been recruited into the artillery, and their medical officer stated that when they reported for duty many of them could not even lift the gun parts, let alone assemble them Many of them needed a course of physical training before they were fit for duty, and most gained a stone in weight in three months of service conditions It may even be that some of those graded I would have been graded II if they had been seen a few months earlier

Figs 4*b* and 5*b* are radiographs showing the typical varieties of flattening seen amongst these men—quite analogous to those seen amongst females (Figs 4*a* and 5*a*), whilst Figs 6*a* and 6*b* show the close similarity between the shape of the male and female brim where definite clinical evidence of rickets was present

TABLE VIII

Pelvic Types in 39 Males from Social Classes III, IV and V All Under 5 ft 6 ins in Height

Pelvic Type	Number	Percentage
Round	16	41
Narrow	2	5
Flat	16	41
Scutiform	5	13
Total	39	100

It is not proposed to discuss the male pelvic brim in detail in this paper but merely to draw attention to the similarity between the effects of height and physique on the pelvis in both sexes Analysis of the male pelves by height and physique gives the same result for the student group and the other men and therefore the results for all available males (a total of 157, 100 students and 57 men from other sources) have been combined

The average difference in height between the male and the female is not known, but the average height of 100 women medical students entering Aberdeen University during the last five years is 5 ft 3½ ins, so that this group, at least, are 5 ins shorter than a comparable group of men

Using this as a guide, roughly corresponding standards for males and females were adopted, the " small " males being under 5 ft 6 ins.

and the "tall" over 5 ft 10 ins in height Table IX shows the incidence of pelvic types among both sexes and shows that in both the incidence of the flat and scutiform types is much greater among both short men and short women

Table X gives the same information about the males as does Table III for females The same general trend is apparent—there are more essentially normal (round and narrow pelves) amongst the physically superior group and many more essentially abnormal pelves (flat and scutiform) amongst those of inferior physique, and, just as among the women, this difference is more evident in those of small stature It should be noted that the incidence of narrow pelves in the small males and scutiform pelves in the tall males is outwith the general pattern, but the small numbers available diminish the importance of this observation As with the females the degree of flattening was considerably

TABLE IX

Pelvic Type Incidence in Both Sexes by Height

Pelvic Type	Males		Females	
	Tall (Height over 5 ft 10 ins)	Small (Height under 5 ft 6 ins)	Tall (Height over 5 ft 5 ins)	Small (Height under 5 ft)
Round	84%	50%	87%	65%
Narrow	4%	4%	6%	Nil
Flat	8%	36%	7%	34%
Scutiform	4%	11%	Nil	1%
Total number of cases	48 (100%)	45 (100%)	100 (100%)	100 (100%)

TABLE X

Pelvic Type Incidence by Physique in Males

	Tall Males			Small Males	
	Grade I	Grade II		Grade I	Grade II
Round	85 0%	77 8%	Normal pelvic shapes	72 0%	38 5%
Narrow	5 0%	0 0%		0 0%	6 5%
Flat	5 0%	22 2%	Abnormal pelvic shapes	21 0%	42 0%
Scutiform	5 0%	0 0%		7 0%	13 0%
Number of cases	39 (100%)	9 (100%)		14 (100%)	31 (100%)

more severe in abnormal pelves of males graded I compared with those of males graded II

Table XI shows the incidence of the pelvic types for males of all heights by physical grade It shows quite clearly that there are very many more flattened pelves in those of Grade II than in those of Grade I The lower table shows that the three indices of curvature are all lower in the poor physical grades A closer study of the actual degree of flattening of the posterior segment showed that, if anything, it is slightly more accentuated in the male than in the female, but certainly not to such a degree as would warrant the designation of a female pelvis as " android " just because it shows a degree of flattening insufficient to be regarded as rachitic

If the actual size of the male pelvic brim as indicated by the area and the true conjugate diameter is examined, again the same trend as seen in the female is apparent Both these measurements increase with height, and both decrease with poor physique irrespective of height On the whole, the measurements are somewhat smaller than those of the female, suggesting that the male pelvic brim is slightly smaller than the female (an observation which has been noted by other workers), but since the size of the pelvis is very dependent on stature, and since no one really knows the actual differences in height between the sexes, it would be very difficult to come to any conclusion about this point

TABLE XI

Incidence of Pelvic Types and Means of Indices of Curvature in 157 Males of All Heights

Pelvic Type	Grade I	Grade II
Round	78%	58%
Narrow	10%	3%
Flat	9%	25%
Scutiform	3%	12%
Total number of cases	90 (100%)	67 (100%)
Brim index	92 5%	86 1%
Sagittal index	36 2%	33 8%
Posterior sagittal transverse index	33 5%	29 3%

The flat and the scutiform pelves were found to be small in the female , the same also applies to the males In this series the average conjugate in the flat pelvis of the male was 9 4 cm (3 7 ins) and in the scutiform 10 9 cm (4 3 ins) In only one of the latter was it high, measuring 12 1 cm (4 7 ins) These shapes, by and large, were only found in small pelves in both sexes

It would thus appear from this investigation that the pelvic brim in both male and female has an essentially similar round or long oval shape in individuals who have grown to full stature, and that such a shape should be regarded as the normal Other shapes which show flattening, *i e* the flat and the scutiform, are found almost exclusively in small pelves and should be regarded as abnormal, produced by poor growth

CLINICAL SIGNIFICANCE

These results should have some obstetric significance A tall patient is almost certain to have a large well-curved pelvic brim which can accommodate a normal infant of any size, and since outlet contraction sufficient to cause serious difficulty in labour is seldom found if the brim is normal, the chances of difficult labour due to abnormality of the pelvis are remote In fact, Cæsarean section for disproportion is extremely rare among women over 5 ft 2 ins in height In the tall group there were 13 forceps deliveries, all easy low outlet forceps deliveries with the exception of one case in which uterine dysfunction was marked and the cervix only three-quarters dilated at the time of delivery Very slight outlet contraction may have been a factor in 6 of the cases, but the indication for delivery was usually uterine inertia, rigidity of the soft parts, fœtal or maternal distress There was, in act, no problem related to the size of the pelvis among these 100 tall women

A small patient from the poorer classes is likely to be of poor physique and to have a small pelvis of abnormal shape If the infant is small—and fortunately it often is—no great problem may arise, but when the infant is a little larger, labour is likely to be difficult In the first labours of this series of 100 small women, 6 Cæsarean sections and 5 difficult mid-forceps deliveries were necessary because of disproportion, so that major mechanical difficulty was encountered in 11 per cent In each case the patient was of inferior physique (Grade II) There were 14 other forceps deliveries in this group, the indications for which were comparable to those among the tall women—uterine inertia, fœtal and maternal distress, and sometimes slight outlet contraction

It is hoped that a further detailed study of the pelvis at all levels in 1000 cases accumulated to date will throw further light on pelvis form and its clinical significance

CONCLUSION

As a result of this preliminary investigation, it may be postulated that

(1) Amongst the well-to-do social classes, as a result of good environment during growth, small women usually reach their optimal height and may be classed genetically small—the true pelvis though smaller than in tall women of the same class is well curved with no evidence of flattening or other distortion

(2) In the less well-to-do, short stature is often the end result of poor environment The stature of a " genetically " small woman is often

still further reduced by poor environment during growth, and in this case the pelvis shows evidence of considerable flattening, especially of the posterior segment superimposed on a generally small pelvis The number of small women in this class is increased by those " genetically " taller but whose short stature is due to poor environment, and these will show a similar deformity of the pelvis which may possibly be a little larger, especially transversely

(3) Tall women in general are of better physique since any defects of environment have been insufficient to disturb general growth to any degree As a rule, the pelvis is large and well curved Deformities at the brim may occur but these are of a minor degree, since growth has not been greatly disturbed, and their significance in obstetrics is negligible

My thanks are due to Professor Dugald Baird for his advice and encouragement, to Mr Aberdein and Miss McEwan, Senior Radiographers of the Aberdeen General and Special Hospitals for their technical assistance, to the Maternity Hospital Almoners, Mrs McGhee and Miss Thompson for their help with social data, and to Miss Grassick for her assistance with much of the documentation I am also grateful to the Medical Research Council for defraying expenses

REFERENCES

[1] CALDWELL, W, MOLOY, H C and SWENSON, P (1939), " The Anatomical Variations in the Female Pelvis and Their Classification according to Morphology," *Amer Journ Rœntgen*, 41, 505

[2] GREULICH, W W, and THOMS, H (1939), " The Study of Pelvic Type and Its Relationship to Body Build in White Women," *Journ Amer Med Assoc*, 112, 485

[3] NICHOLSON, E, and ALLEN, H SANDEMAN (1946), " Variations in the Female Pelvis," *Lancet*, 2, 192

[4] ALLEN, P (1947), " Standardised Radiological Pelvimetry," *Brit Journ Radiol*, 20, 45, 108, 164, 205

[5] MOIR, J CHASSAR (1946), " The Use of Radiology in Predicting Difficult Labour," *Journ Obstet Gynæc Brit Emp*, 53, 487

[6] CHASSARD and LAPINE (1923), " Etude radiographique de l'arcade pubienne chez la femme enceinte une nouvelle methode d'appreciation du diametre bi ischiatique," *Journ de Radiol et d'Electrologie*, 7, 113

[7] SHAPIRO, H L (1939), *Migration and Environment A Study of the Physical Characteristics of the Japanese Immigrants to Hawaii and the Effects of Environment on their Descendants* London Oxford University Press

[8] BAIRD, D (1949), " Social Factors in Obstetrics," *Lancet*, 1, 1079

[9] STEELE, K B, and JAVERT, C T (1942), " Classification of the Obstetric Pelvis Based on Size and Mensuration and Morphology," *Amer Journ Obstet Gynec*, 44, 783

[10] THOMS, H, and GREULICH, W W (1940), " A Comparative Study of Male and Female Pelves," *Amer Journ Obstet Gynec*, 39, 56

[11] INCE, J G H, and YOUNG, M (1940), " The Bony Pelvis and Its Influence on Labour," *Journ Obstet Gynæc Brit Emp*, 47, 130

Discussion

Dr Fahmy (Edinburgh) found it difficult to believe that a genetic factor was not responsible, to some degree, for a woman's stature, and suggested that useful information might be obtained, in this respect, from an examination of the mothers of the young girls already investigated by Dr Bernard He noted that the android pelvis was seldom seen in Edinburgh

Dr de Soldenhoff (Irvine) discussed the value of X-ray pelvimetry as an aid to delivery He believed that in most cases sufficient information could be obtained from clinical examination, including estimation of height X-ray pelvimetry should be restricted to selected patients and even then limited to the lateral view

Dr Liston (Edinburgh) thought that if pelvic development was influenced by dietetic factors there should be similar evidence of maldevelopment in the other bones of the body General assessment of the patient should give valuable information concerning pelvic shape Size of feet varied in proportion to height and he had noted that short stocky fingers were sometimes associated with pelvic abnormality

Dr Black (Lanark) believed that the stage of growth during which malnutrition occurred might well affect the type of pelvic abnormality thus with early malnutrition flattening of the pelvis might result whereas with later malnutrition the deformity might be of the android type

The President, *Professor Dugald Baird* (Aberdeen), referred to the growth of the present generation which resulted in sons growing much taller than their fathers He considered that height was a good index of nutrition and a valuable clinical guide as it was easy to estimate It was difficult to define exactly the difference between a rickety flat and simple flat pelvis In London many women had flat pelves with the contraction due to poor nutrition Was this not in fact similar to the pelvis in Scotland in which the changes were attributed to rickets? He advised routine measurement of height at the antenatal clinic in order to obtain an idea whether there was likely to be difficulty or not during labour

Dr Duncan and *Dr Lindsay* also took part in the discussion

In replying, *Dr Bernard* said that he did not intend to be dogmatic on the relative importance of genetic influences and of environmental influences on stature Both undoubtedly contribute to the adult stature attained Whilst routine pelvimetry was useful for academic purposes and clinically helpful in small women many of these would have uncomplicated spontaneous deliveries

The Transactions
of the
Edinburgh Obstetrical Society

SESSION CIV.—1951-1952

A CONSIDERATION OF STERILITY FACTORS IN THE LIGHT OF SUBSEQUENT PREGNANCIES

I Factors in the Female

By G DOUGLAS MATTHEW, F R C S E, M R C O G, and
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WE are indebted to the *Reports of the Biological and Medical Committee* published earlier this year for the latest estimate of involuntary childlessness in this country We note that the work of this committee formed part of a general investigation by the Royal Commission on Population, but we submit that when it comes to dealing with the childless couple our thoughts are far removed from the evil consequences of depopulation We prefer to think that the problem is of a more personal nature closely linked with the happiness of the would-be parents The figures arrived at can be regarded only as approximate but the estimates of 8 per cent likely to be involuntarily childless, 4 5 per cent restricted involuntarily to one child and a further 5 5 per cent so restricted to two children give some idea of the magnitude of the task confronting those who elect to seek the cause of this state of affairs In recent years this matter has attracted the attention of many gynæcologists and urologists and others, and has provided the material for countless publications and many conferences In fact, so numerous and extensive are the implications and ramifications of this subject in all its aspects embracing etiology, investigation and treatment that it is beyond the scope of this paper to do more than present to you certain conclusions which we have reached as a result of four years' experience in this field The evidence for these conclusions is chiefly provided by a number of patients whose patience and fortitude whilst undergoing investigation were rewarded by pregnancy and, to a lesser extent, by a larger number of patients, who, so far, have been less fortunate

Analysis of 107 Pregnancies

For the purpose of this study a consecutive series of 107 pregnancies occurring in patients investigated and treated in our sterility clinic has been reviewed The cases have been divided into three groups primary sterility, secondary sterility and habitual abortion

Primary Sterility

In this group there were 70 pregnancies The average age of the patients was 29 years, the youngest being 21 and the oldest 41 years

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Papers read to the Edinburgh Obstetrical Society on Wednesday, 13th December 1950

Average length of time of marriage was four years eight months, the shortest period being fifteen months and the longest twelve years Because of the intrusion of the war years, affecting most marriages, it has been difficult to estimate accurately the exact duration of effective married life Taking into account war service and the practice of contraception, we found that the average period of effective marriage was three years and eight months Contraception had been practised by only 20 per cent of these patients Apart from the isolated case of fifteen months' marriage, investigated on account of age, this would appear to be a typical series of cases of primary sterility

Investigation revealed definite etiological factors in 68 cases Thus in only 2 cases no obvious cause to account for the period of infertility could be discovered and in 75 per cent of patients more than one factor was discovered The average frequency of coitus was found to be *five times per month* Those *conditions considered to contribute* towards the state of infertility are summarised and grouped under six headings according to whether the factors are general, local, cervical, endometrial, tubal or male

ETIOLOGICAL FACTORS

General Factors

	Number of Cases
Malnutrition and obesity	8
Infrequency of intercourse .	4
History of previous appendicitis (six appendicectomies)	7

Local Factors

	Number of Cases
Polycystic ovaries	10
Intact hymen	4
Hypoplasia	4
Retroverted uterus	3
Trichomonas vaginitis	2

Cervical Factors

	Number of Cases
Chronic infection	20
Deficient secretion	7
Hypoplasia	4
Displacement by retroversion	3
Tight internal os	3

Endometrial Factors

	Number of Cases
Recurrent amenorrhœa	1
Recurrent amenorrhœa with occasional anovular cycles	1
Irregular menstruation with occasional anovular cycles	1
Regular menstruation with occasional anovular cycles	1

Tubal Factors

	Number of Cases
Inactive patency	11
Obstruction	9
Spasm	8